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# ORIGINAL ARTICLES

## GUMMA OF THE PITUITARY ASSOCIATED WITH LESIONS IN THE SPINAL CORD WHICH MAY REPRESENT EARLY LESIONS OF SYRINGOMYELIA*

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IN the case which I shall report, two interesting lesions were found; one, a gumma of the pituitary, the other, a condition which possibly represents an early stage of syringomyelia. It is reported first because of the infrequence of both lesions, and second because of the interest that attaches, always, to early stages of processes which lead to clinical complexes. I regret the brevity of the history. It is possible that, under other circumstances, a more complete one could have been obtained, and it is possible also that some symptoms might have been discovered which could have been of interest in connection with the lesions.

The patient was one R. B., a colored male, aged 52. He was admitted to the Cincinnati General Hospital (No. 190,172) on December 7, 1914, when he offered the complaint of pain in the stomach and sore throat. The family history was not taken. In childhood he had had measles and mumps; in his adult years he had contracted typhoid, pneumonia, influenza, gonorrhea and syphilis. He had been an excessive smoker, but denied alcohol and other drugs.

The illness which resulted in his application for admission to the hospital began, he said, about three weeks before admission (November 15, 1914), at which time, he said, he had pain in the stomach accompanied by vomiting. At that time he had a sore area on his right leg about the ankle. He also had a "lesion" on the soft palate. He "did not speak plain." The occipital region of the scalp was normal. While in the ward he had a good appetite.

That is the extent of the history. There was no note of any symptoms nor of any treatment. No clinical diagnosis was made.

The patient died eight days after admission (December 15, 1914), and the post mortem was made eighteen hours after death. The weather was cold, and the body remained in a good state of preservation.

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The following is the autopsy protocol:

The body was that of a colored man of apparently about 55 years of age. It weighed about 160 pounds and was in a good condition of nutrition. There were some old, irregular, partially healed, sluggish, ulcerated patches on the right shin near the ankle. The scalp was the seat of a generalized alopecia, so that it was almost completely bald. The skin of the areas of alopecia was white, pearly or opalescent in appearance and diffusely thickened. The pupils were equal, and neither dilated nor contracted. There was no edema of the legs. The peripheral lymph glands were not noticeably enlarged, though shotty to the touch.

When the scalp was stripped from the calvarium, an abundant serous fluid ran from the vascular foramina of the bones, and when the skull-cap was removed it was found that the dura and the membranes beneath it were filled with an extraordinary amount of a clear serous fluid. The dura was congested, the pia was not, but the latter was so saturated with fluid that, after removal of the dura, it stood up in blebs. There were no unusual adhesions between the membranes. The venous sinuses were not distended with blood. The convolutions were rather flat. The whole brain was pale, and showed no evident increase in consistency. It was placed at once in ten per cent formalin. Later it was examined and showed nothing macroscopically wrong, except that the pia was more than normally adherent. The falx was almost completely ossified from about the middle of the median fissure to the crista. The ventricles were not dilated. The chorioid plexuses appeared healthy. The sinuses were patent but about them the dura was thickened.

The same condition, which was noticed in the membranes of the brain, existed also in those of the cord, i. e., a tremendous edema. The cord was fixed in formalin and later was examined. It then appeared that the meninges were more than usually adherent and that in the pia here and there were spicules and platelets of bony material. There were no distinct macroscopic lesions in the cord.

The pituitary gland was removed and during this operation, which was difficult because of adhesions about it, it ruptured and disclosed a thick, yellowish, almost caseous material, which seemed to involve almost all of the organ, which was finally removed together with part of the sellar bone.

When the thorax was opened, the lungs did not collapse because of the presence of old bilateral adhesions. On the left side these adhesions were mostly apical and posterolateral. On the right, they were general. On both sides the lobes were adherent by old adhesions. There was no fluid in the pleural cavity. The thyroid was apparently normal. The thymus was atrophic. The bronchial glands were enlarged, succulent, deeply pigmented and edematous. The mediastinal tissues generally were edematous. Section of the lungs showed no apparent abnormality save a more or less generalized fibrosis, localized chiefly under the pleura.

The heart and thoracic aorta were removed *en masse*. The heart itself was atrophic and beneath the epicardium was a considerable increase in fat. The cavities were filled with a clotted, red, friable mass; the valves were apparently normal. The aorta was the seat of a well marked syphilitic aortitis in all stages of progress, from the early succulent pearly condition to a very distinct atheroma with calcification in placques. In the ascending aorta, about

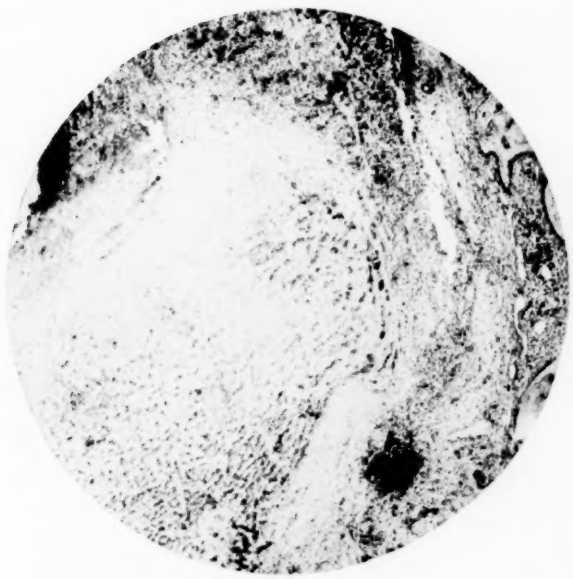


Fig. 1.—A portion of the gummatous lesion in the pituitary, showing also a remnant of pituitary gland, and a small miliary gumma. (By Dr. Charles Goosmann.)

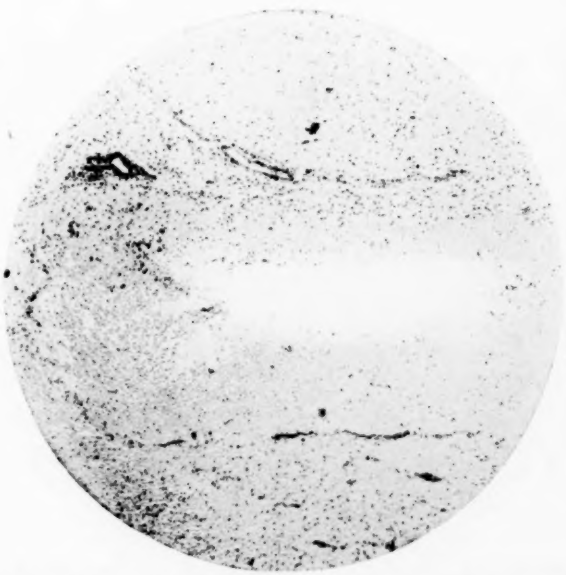


Fig. 2.—A section of the cervical cord showing an area of necrosis which has apparently occurred in a luetic focus. (By Dr. Charles Goosmann.)

half way between the valves and the arch, was a saccular aneurysm, incomplete in form, which projected posteriorly and mesially, pressing upon the pulmonary artery which was bulged inwardly. This sac was about the size of half a hen's egg. Just beneath it was a smaller and more incomplete projection representing also an imperfect aneurysm. Upon the edges of the larger sac and also upon the edges of occasional atheromatous areas were masses of fine recent vegetations.

As one passed down the aorta, the atheromatous process became less well marked until in the abdominal aorta it was almost absent,—there being represented merely by some fatty degeneration in the intima. The process was, then, limited chiefly to the arch of the aorta and to the ascending portion. The sinuses of Valsalva were not involved to any considerable extent. The celiac axis and its branches were involved in the arteriosclerotic process and the renals also were involved to a less extent. The myocardium was pale and rather thin, particularly at the apex. The coronary vessels were slightly sclerotic.

The kidneys were small—each weighed 100 grams. They were pale, the capsules were adherent, the surfaces were roughened. The cortices were thin; the line of demarcation between the cortex and medulla was distinct; the glomeruli could be seen as small, glistening, translucent points and were not congested. There was a slight increase in renal pelvic fat. The ureters were apparently normal. The suprarenal bodies were cavitated. The bladder and prostate were apparently normal. The abdominal organs lay in their normal positions, and, except for the fact that the sigmoid was somewhat redundant, there was no obvious abnormality.

The appendix was long, patent and ran directly across the peritoneal cavity, reaching about an inch to the left of the spinal column. There was no obvious abnormality discovered in the stomach nor in the intestines.

The pancreas was apparently normal.

The spleen weighed 75 grams. It was atrophic, but aside from a moderate sclerosis, showed no obvious abnormality. The peritoneal lymph glands were not obviously enlarged. They were firm and congested.

The liver (900 grams) was atrophic and soft, though not increased in friability, and had a generally reddish color. Upon the surface were several stellate scars, the larger one occupying the central part of the right lobe. At the tip of this scar, in the substance of the liver, was a small caseous area forming the apex of the scar. Another stellate scar appeared at about the middle of the right lower edge of the liver which was deformed so that a notch was formed at this point. At the apex of this scar, also in the substance of the liver, was a yellowish, apparently caseous, area. Upon cutting the liver, the surface showed nothing more than a general reddening,—a moderate congestion,—with some slight increase in fibrous tissue. Along the portal vessels was a decided increase in fibrous tissue which had a rather pearly appearance, almost cartilaginous. The gall bladder contained a thick mucoid, pale, yellowish-colored bile.

*Anatomic Diagnosis.*—Edema of the brain and the meninges; Chronic diffuse nephritis with secondary contraction (arteriosclerotic); Aortic atheromatosis with aneurysm formation; Generalized arteriosclerosis; Syphilis (gummatous) of the liver; Syphilitic lesion (gumma) in the pituitary.

*Microscopic Diagnosis.*—Gummatous (luetic) hypophysitis; and hepatitis;

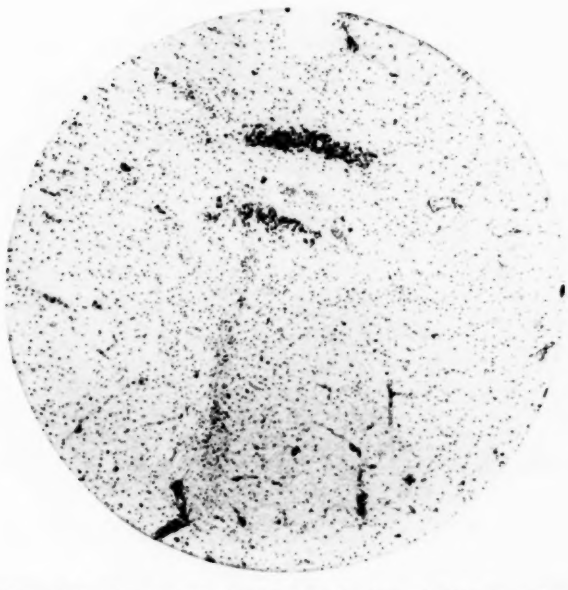


Fig. 3.—A section of the dorsal cord showing a collection of cells posterior to the central canal and its group of hyperplastic cells. (By Dr. Charles Goosmann.)

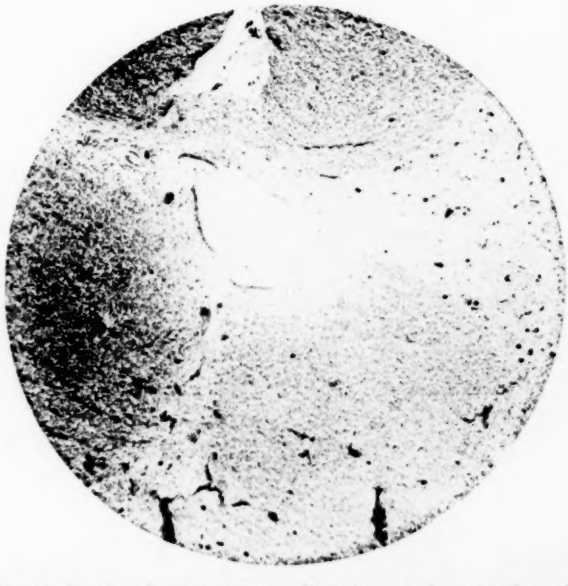


Fig. 4.—Section of the dorsal cord showing dilatation of the central cord. (By Dr. Charles Goosmann.)

Chronic diffuse nephritis, renal arteriosclerosis; Syphilitic dermatitis; Pancreatic fibrosis; Congestion of the spleen; kidney, liver, and pancreas. Degenerative (luetic?) lesions in the spinal cord.

In the following remarks on the histologic changes, attention is focussed upon the pituitary and the spinal cord, for there seems to be no obvious value in detailing the changes in all the other organs. Concerning these, it will suffice to say that the hepatic lesions were typically syphilitic, and that the aortic ones were typical of a luetic mesaortitis.

The sections showed that except for a small area of glandular tissue, the pituitary was almost replaced by a mass of gummatous tissue which was in large part necrotic (Fig. 1). Beyond this main lesion there were other smaller, more recent, younger, gummata, lying at the periphery of the larger lesion and beyond it in connection with the periosteum of the sellar bone which was the seat of a syphilitic periostitis. In none of these sections were tubercle bacilli found.

The following are notes on the cord lesions:

*Sections made from the cord 32 c.m. from the tip of the cauda.*—In these there is a general dilatation of the blood vessels of the anterior median fissure. The substance of the anterior commissure is edematous and in it there is a decided increase of small round cells of glial origin. The region of the central canal is represented by a mass of hyperplastic cells which, from their appearance, have originated in canal epithelium, and the central canal is represented by a mere slit. Posterior to this mass of cells are dilated blood vessels, posterior to which is an area lying to one side of the line of the posterior fissure which is apparently both edematous and necrotic. This area extends laterally and posteriorly, but chiefly laterally, and almost parallel to the line of the commissure. At its median extremity, which is broader than at any other point, a blood vessel appears, and about it there are a considerable number of round cells. In this neighborhood there is less necrosis and more edema, but laterally the round cells become scant in numbers, and the necrosis increases, until almost as the posterior horn is reached, the number of cells increases and necrosis decreases. Whether or not the above description is successful, the picture is one which suggests a linear focus of hyperplasia of glia tissue with central necrosis, and in some respects has a certain resemblance to what one might expect of a luetic focus. The tissue on the opposite side of the posterior fissure presents no such picture, and except for evidence of mild edema, appears normal (Fig. 2).

*Sections made 19 c.m. above the tip of the cauda.*—In these sections the commissure is generally edematous and more evidently so than in those taken higher in the cord. In this section the blood vessels are not only dilated but are surrounded by a clear zone in which there is considerable coagulated protein. The central canal appears as a small space surrounded by a complete epithelium, but laterally, for some distance, there are masses of hyperplastic cells springing evidently from the cells of the central canal. There is a second collection of these cells posterior to the first and separated from it by a very edematous tissue containing dilated blood vessels (Fig. 3). Extending from a point midway between and lateral to these two masses of hyperplastic cells is an area of degeneration within which there are corpora amylacea.

*Sections made 18 c.m. above the tip of the cauda.*—In these the central

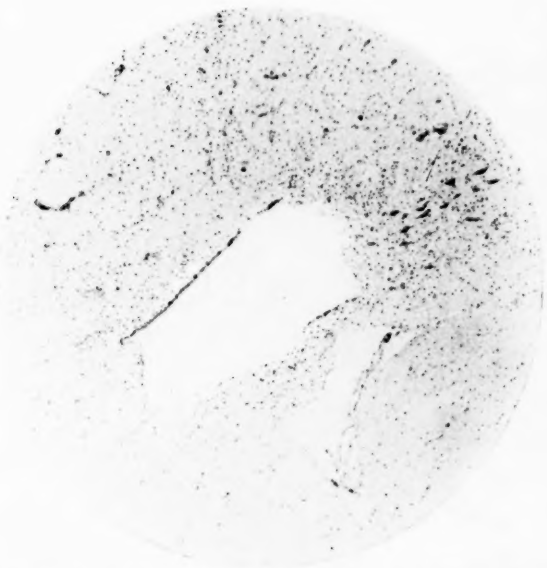


Fig. 5.—Section of the dorsal cord showing dilatation of the central cord. (By Dr. Charles Goosmann.)

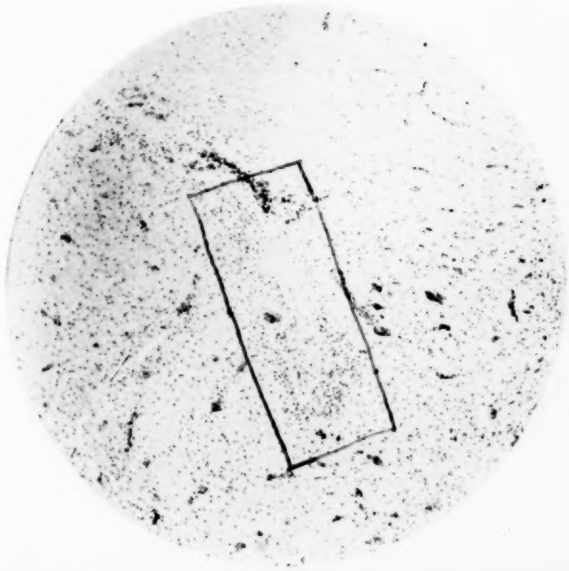


Fig. 6.—A section of the dorsal cord showing a linear or somewhat fan-shaped area latero-posterior to the central canal which is bounded by hyperplastic glial cells, and which shows a central area of degeneration. (By Dr. Charles Goosmann.)

canal is considerably dilated (Figs. 4 and 5) and lined with a cuboidal, or even a flat cuboidal epithelium. About it are a moderately increased number of small round cells.

*Sections made 17 c.m. above the tip of the cauda.*—In these sections there is again hyperplasia of central canal cells extending laterally from a small central canal, about which there is very distinct edema, associated with vascular dilatation. Extending postero-laterally from region of the central canal is a linear area almost destitute of cells in its center but surrounded by small round glial cells which are arranged in irregular columns which rest upon the degenerated area and extend at right angles to it (Figs. 6 and 7).

*Sections taken from 16 c.m. above tip of cauda.*—In these sections there appear to be two central canals, one in the usual position, and one lateral to it.

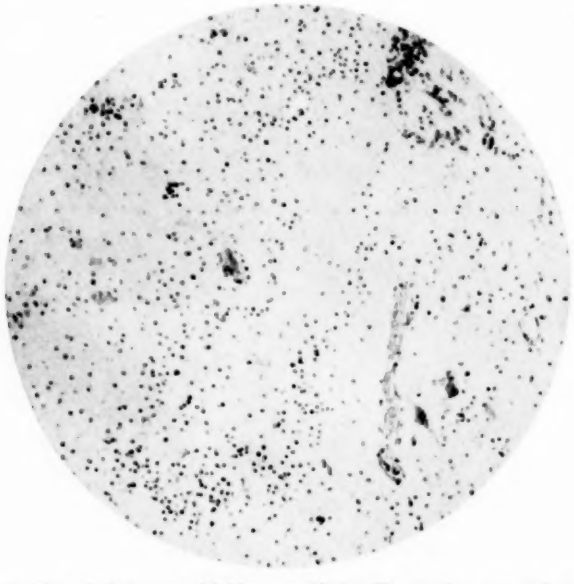


Fig. 7.—Same as Fig. 6, but more highly magnified. Shows the area referred to under Fig. 6. (By Dr. Charles Goosmann.)

The one is large, dilated and lined with low columnar and cuboidal epithelium; the other is small and lined with apparently normal epithelium. Between the two there are a few epithelial cells. There is, in these sections, no evidence of necrosis.

*Sections taken 10 c.m. above the cauda.*—In these, there is no evidence of a central canal but at its usual location is a collection of cells of central canal origin. Posterior to this cell mass and running posteriorly and laterally, is a linear area of gliosis which looks much like a scar. In it there is evidence of degeneration of a slight degree (Fig. 7).

## Discussion.

The meaning of these changes is not entirely clear, but looked at in one way, they suggest that in this case, syphilis, in addition to the lesions of the parenchymatous organs and of the pituitary, has also affected the spinal cord so that here and there hyperplasias of the cells of the central canal have been

initiated and have given rise by pressure to scattered dilatations of the central canal, with the production of a mild grade of hydromyelia. They also suggest that the same luetic process has been limited at certain foci which appear as linear areas of gliosis, with or without central necrosis.

If one wishes to assign the spinal lesions to one of the categories into which all cases of well-developed syringomyelia are grouped, one must choose that in which the primary syringo-myelias are placed. This case does not (provided it is actually an early stage of syringomyelia) belong in the group of neuro-epithelial glioses; it is not the result of diverticula of the central canal; there is

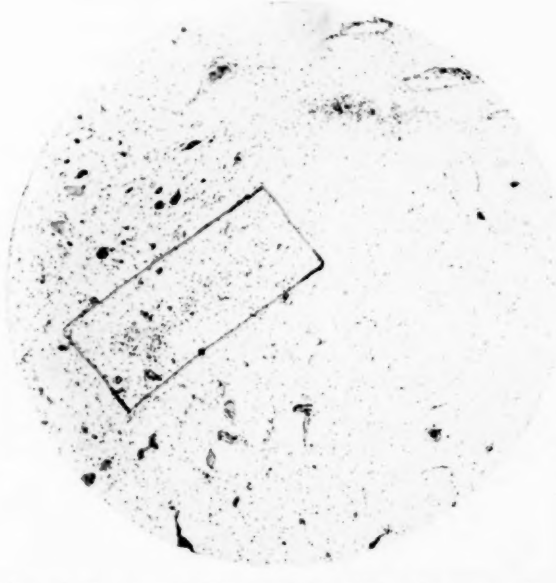


Fig. 8.—A section of the upper lumbar cord in which there was obliteration of the central canal and an area of gliosis postero-lateral to the region of the central canal. (By Dr. Charles Goosmann.)

no evidence of an anomaly of closure of the posterior sulcus, and there is no evidence that the lesions are the result of degeneration in gliomas.

## Conclusion.

1. A case is reported in which there are certain lesions in the pituitary and in the spinal cord which, it is suggested, have a common etiology.

2. The lesion in the pituitary is definitely luetic. Those in the cord are possibly luetic.

3. The cord lesions seem to suggest that they represent an early stage of syringomyelia.

## LITERATURE.

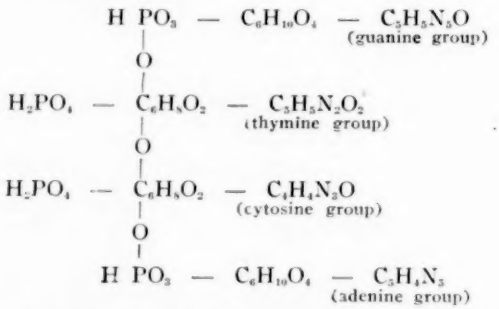
Klotz: Amer. J. Med. Sc., 1913 (146) 681. (Lit. on Syringo-myelia.)
Stroebe: Zieg. Beitr., 1905 (37) 455. (Lit. on Gumma of the Pituitary.)

# SOME FEATURES OF PURINE METABOLISM*

By H. Gideon Wells, M.D., Chicago, Ill.

THERE is much justification for the statement with which Walter Jones prefaces his splendid review of the nucleic acids,[1] "The nucleic acids constitute what is possibly the best understood field of Physiological Chemistry." The success with which chemical investigators have disentangled the many complex problems presented by the nucleoproteins is indeed remarkable, in view of the great difficulty of the task, and it is no small source of satisfaction to be able to record that much of the recent progress, built upon the fundamental studies of Miescher, Kossel and Emil Fischer, has been made in American laboratories, especially those of Walter Jones and P. A. Levene. We now have a definite understanding of the structure of nucleic acid, and we are able to state with some assurance the steps by which it is disintegrated in the animal body, a knowledge that has been given to us within a relatively short time. It is my purpose to present mainly certain aspects of purine metabolism that have been under investigation in my own laboratory for some years, although, to make clear some of the points involved, I shall need to preface the discussion of our work by a brief recapitulation of the newer facts concerning the chemistry and metabolic career of nucleic acid.

A long series of careful analytical studies has at last shown us that nucleic acids are, whatever the source, quite similar in composition, consisting always of a complex containing phosphoric acid, the two amino purines (adenine and guanine), two pyrimidines (either cytosine and uracil or cytosine and thymine); and a carbohydrate, which may be either a pentose or a hexose. Apparently there are two sorts of nucleic acids, one from plants, which contains always uracil and pentose, and one from animal tissues, containing instead thymine and a hexose. So constant are the findings in regard to these compounds that it has seemed feasible to consider their manner of union in the intact nucleic acid molecule, and Levene and Jacobs have proposed as the structure of thymus nucleic acid the following arrangement:




It will be seen that this proposed formula postulates in the nucleic acid

*From the Department of Pathology, University of Chicago, and the Otho S. A. Sprague Memorial Institute. Presented to the Chicago Society of Internal Medicine, Oct. 25, 1915.

[1]Nucleic Acids, their Chemical Properties and Physiological Conduct. Monographs on Biochemistry, Longmans, Greene & Company, 1914.

molecule, one radical of each of the two purines and pyrimidines, each of these being united by a carbohydrate radical to a phosphoric acid radical. Recognizing that this must be looked upon as a provisional formula, it will serve as a base of departure from which to consider the metabolism of nucleic acid.

The grouping of hexose + purine or hexose + pyrimidine is referred to as a "nucleoside," analogous in terminology to "glucoside." The same groupings plus the phosphoric acid radical constitute the "nucleotids," nucleic acid thus being made up of four neucleotids. Within the past year Emil Fischer has reported[2] the synthetic production of a nucleotid, composed of phosphoric acid united to a glucoside of theophyllin, this really constituting the long-sought synthesis of a nucleic acid, even though the artificial product is not the same as any known to occur in nature. With these facts before us we may consider the manner in which nucleic acids are disintegrated in the animal body.

So large a molecule can conceivably be disintegrated in many different ways; that is, the lines of cleavage might pass through several different points and in many different orders, but there is evidence available which causes us to believe that the process is quite constant in animal metabolism. Jones considers it probable that the first step is a decomposition of the tetranucleotid into dinucleotids, and that these are in turn split into mononucleotids. Little is known about the subsequent career of the two pyrimidine nucleotids, but we have an abundance of information concerning the nucleotids containing the purines, and it is in these our present interest lies. Each nucleotid has two points at which it might be split, and we have reason to believe that there exist in animal tissues enzymes which may specifically attack each bond. One enzyme separates the phosphoric acid radical from the nucleoside, thus:

$$\underset{\text{guanylic acid}}{H_2PO_4 - C_5H_8O_5 - C_5H_4N_5O} + H_2O \xrightarrow[\text{phospho-nuclease}]{} H_3PO_4 + \underset{\text{guanosine}}{C_5H_9O_4 - C_5H_4N_5O}$$

and this enzyme is therefore designated as *phospho-nuclease*.

Another enzyme, *purine nuclease*, splits off, instead, the purine radical, thus:

$$\underset{\text{guanylic acid}}{H_2PO_4 - C_5H_8O_5 - C_5H_4N_5O} + H_2O \xrightarrow[\text{purine-nuclease}]{} H_2PO_4 - C_5H_9O_4 + \underset{\text{guanine}}{C_5H_5N_5O}$$

Following either of these cleavages, the enzymes which deaminize purines begin to act, and we have formed as a result either the free oxypurines or the oxypurines still bound in the glucoside-like combination with sugar. If the purines are free the reaction will be:

$$\underset{\text{guanine}}{C_5H_5N_5O} + H_2O \xrightarrow[\text{guanase}]{} \underset{\text{xanthine}}{C_5H_4N_4O_2} + NH_3$$

or, in case the guanine glucoside is present:

$$\underset{\text{guanosine}}{C_5H_9O_4 - C_5H_4N_5O} + H_2O \xrightarrow[\text{guanosine-deaminase}]{} \underset{\text{xanthosine}}{C_5H_9O_4 - C_5H_3N_4O_2} + NH_3$$

In the latter case a hydrolytic enzyme, xanthosine-hydrolase, then splits off

[2]Sitzungsber. k. Akad. Wissenach., Berlin, 1914, xxxiii, 905.

tissues, they contain no adenase which will deaminize free adenine. Furthermore, secondary tumors in the liver do not acquire the xanthine-oxidase which is present in human liver, but breed true to the parent cells. Tumors in the lower animals also present the enzymes characteristic of the corresponding tissues of these animals, at least to a certain extent, but they exhibit chemically their embryonal character as well as they manifest it microscopically. Thus, a primary carcinoma of the liver in sheep contained guanase and adenase, but no xanthine-oxidase or uricase; corresponding to the early fetal rather than to the adult sheep liver in lacking uricase and xanthine-oxidase. It is interesting to note also that in one instance we were able to obtain by an examination of the purine enzymes valuable evidence as to the origin of a certain tumor when histological evidence was inconclusive. This was in a rather common type of primary tumor of the sheep liver, which, on account of both its histological and gross characteristics has been believed by some to be of adrenal origin, that is, hepatic hypernephroma. In such tumors Long[4] found adenase, an enzyme present in sheep livers but not present in either adrenal or kidneys of sheep, a fact which indicates that these tumors are not of adrenal or renal origin, but derived from the liver cells.

As yet we know nothing concerning the modifications which disease may produce in the purine enzymes, and the effects such modifications may have on metabolism. Quantitative studies of enzyme activity of tissues are seldom if ever of value, and we have no evidence that in any pathological conditions there occurs an absolute loss of any of the purine enzymes. On the contrary, I found that the liver of animals poisoned with phosphorus and hydrazine, so that a maximum degree of fatty degeneration was produced, showed quantitatively the same uricolytic activity as normal livers.[4a] On the other hand, in liver tissue between cancer nodules there has seemed to be a decreased xanthine-oxidase activity; and in the bladder of a tuberculous monkey I found an appreciable amount of uric acid, whereas normal monkeys destroy practically all the uric acid and excrete little purine but allantoin.

As we have mentioned before, the human organism is peculiar in the lack of demonstrable uricolytic activity in any of its tissues. This fact has been established conclusively by the concordant results of several independent observers. The presence or absence of uricase is a very definite thing which permits of no possibility of error, for when present the action of uricase is strong and rapid. Thus, in an experiment with cat liver, it was found that this tissue destroyed completely one-twentieth of its weight (estimated as water-free tissue) in 2½ hours under laboratory conditions. Other livers were found fully as active. In view of the demonstrated presence of uricase in several mammals, it seemed desirable to determine as completely as possible just the distribution of this enzyme in nature. Studies of many different species did not reveal its presence outside the mammals. Among the mammals all the common domestic and laboratory animals, including also a marsupial, the opossum, showed uricase in some tissue, usually the liver.

On account of the peculiar exception of man in this respect, we secured tissues from different species of monkeys, and found that they too possessed

[4] Jour. Exp. Med., 1913, xviii, 512.
[4a] Jour. Exper. Med., 1910, xii, 607.

active uricolytic enzymes in the liver tissue, thus resembling the lower mammals rather than man. At this stage of our work we were fortunately able to bridge the gap in our studies through the kind assistance of Dr. W. T. Hornaday, who placed at our disposal the body of a chimpanzee and also of an orang-utan in fresh condition. In each of these animals we found, as in man, a total lack of uricase.[5] Hence these two anthropoid apes stand together with man apart from all other animals in their deficiency in uricolytic enzymes demonstrable by *in vitro* experiments. It is of particular interest that we find here the anthropoids resembling man, while the monkeys resemble the lower mammals, since this observation furnishes a new corroboration of other biological facts indicating that the anthropoids are more closely related to man than to the monkeys. And it is a striking fact that in this particular respect man and the anthropoids are less highly developed than all other mammals, for, as pointed out previously, the uricase is a late development in the animals that possess it, and apparently is the last acquisition in purine metabolism in the course of the development of the animal kingdom. So far as purine metabolism is concerned, man and the anthropoids rank in development with birds, reptiles, and some mammalian fetuses at about full term.

How well the results obtained by the examination of tissue extracts for purine enzymes agree with the metabolic characteristics of the several species of animals, is shown by the accompanying table prepared by Hunter and Givens.[6]

PER CENT OF PURINE-ALLANTOIN

| Order and Species | Allantoin | Uric Acid | Bases | Uricolytic Index | Purine Coefficient |
|---|---|---|---|---|---|
| MARSUPIALIA | | | | | |
| Opossum | 76.0 | 19.0 | 6.0 | 79 | 4.1 |
| RODENTIA | | | | | |
| Rabbit | | | | 95 | 26.0 |
| Guinea-pig | 91.0 | 6.0 | 3.0 | 94 | 27.0 |
| Rat | 93.7 | 3.7 | 2.7 | 96 | 37.0 |
| UNGULATA | | | | | |
| Sheep | 64.0 | 16.0 | 20.0 | 80 | 8.0 |
| Goat | 81.0 | 7.0 | 12.0 | 92 | 17.0 |
| Cow | 92.1 | 7.3 | 0.7 | 93 | 18.0 |
| Horse | 88.0 | 12.0 | 0.5 | 88 | 3.7 |
| Pig | 92.3 | 1.8 | 5.8 | 98 | 12.0 |
| CARNIVORA | | | | | |
| Raccoon | 92.6 | 5.4 | 2.0 | 95 | 16.0 |
| Badger | 96.9 | 1.9 | 1.2 | 98 | 28.0 |
| Dog | 97.1 | 1.9 | 1.3 | 98 | 29.0 |
| Coyote | 95.6 | 2.6 | 1.8 | 97 | 23.0 |
| Cat | | | | 97 | |
| PRIMATES | | | | | |
| Monkey | 66.0 | 8.0 | 26.0 | 89 | 4.5 |
| Chimpanzee | | | | 0 | |
| Man | 2.0 | 90.0 | 8.0 | 2 (?) | 2.5 |

This demonstrates that all mammals as yet investigated, except only man and the anthropoids, excrete allantoin as the chief end product of their purine metabolism. The animals in whose tissues uricolytic enzymes have been found destroy nearly all the uric acid produced in metabolism, while the animals in which no uricase can be demonstrated show no capacity to destroy uric acid. Although human urine does contain minute quantities of allantoin this probably

[5]Jour. Biol. Chem., 1914, xviii, 157.
[6]Jour. Biol. Chem., 1914, xviii, 403.

does not represent a product of metabolism, for Ackroyd has found that ordinary foods contain traces of allantoin, and neither human nor other animal species seem able to destroy any allantoin they may form or receive preformed. Injected or ingested allantoin is excreted quantitatively in the urine.

As Jones has pointed out, the famous analysis of 10,000 liters of human urine by Kruger and Salomen yielded results that exactly agree with what might be expected from our knowledge of the location of the purine enzymes in the human body. They found that, besides the greatly predominating uric acid, the normal urine contained a little xanthine, somewhat less hypoxanthine, and much less adenine, the proportions being 10.1, 8.5 and 3.5, respectively; there was no guanine at all. Now since every human tissue has been found to contain guanase, the absence of guanine from the urine should be expected; and since guanase forms xanthine from guanine, and since xanthine-oxidase is present only in the liver, we should expect a considerable amount of the xanthine that is formed in the tissues to be excreted by the kidneys before reaching the liver, thus explaining the relatively high proportion of xanthine found in the urine. As the tissues in their metabolism can produce hypoxanthine from adenosine we should expect likewise a considerable amount of hypoxanthine in the urine, which was found. The small amount of adenine that was found also fits perfectly the fact that adenine cannot be destroyed in the human tissues, nor yet be formed from nucleic acid, hence a little adenine from the food should appear in the urine.

In view of all these striking agreements of fact and theory we believe that we are justified in applying the results of our *in vitro* experiments to the living organism, at least in part. We therefore seem entitled to say that the human organism cannot destroy uric acid, for it lacks uricase and excretes nearly all its purines as uric acid, and probably none as allantoin. In accord with this, several observers have found that uric acid injected into man is excreted quantitatively and unchanged in the urine. Furthermore, it has been shown that allantoin cannot be destroyed in the human body, and hence the nearly complete absence of allantoin in human urine seems to show that uric acid is not destroyed, at least by conversion into allantoin which seems to be the method used by all mammals that do destroy uric acid.[7]

But the question remains open: May not the human organism destroy uric acid by some other route than over allantoin. Evidence has been advanced in support of the hypothesis that at least part of the nucleoproteins of food can be destroyed by the human tissues, and, in view of the lack of evidence that human tissues can destroy uric acid it may be that some of the purines can be destroyed by some other route. Thus, free adenine cannot be destroyed by human tissues, yet when bound in the nucleoside, adenosine, as it occurs in nucleic acid, it is completely deaminized to hypoxanthine. We can easily imagine that bound purines may be disintegrated while still bound, and with the forma-

[7]Schittenhelm (Zeit. Exp. Med., 1914 (3) 397) who has consistently contended that uric acid is destroyed in the human body (in spite of the refutation of some of his experimental demonstrations of uricolytic activity in human tissues), has recently advanced another sort of evidence in favor of his main theme. He analyzed the lungs, liver, spleen and heart of a man who died after 6 days complete suppression of urine from bilateral thrombosis of the renal veins, and found all told but 0.01 g. uric acid. This finding is capable of the interpretation that uric acid can be destroyed in the human body, since otherwise an accumulation of uric acid should have occurred because of defective renal excretion. There are other possibilities to be considered, however, and the observation needs repetition to establish its value.

tion of some other end products than allantoin. A. E. Taylor,[8] for example, has found that when the metabolism of a man is very completely studied and controlled, the ingestion of a certain amount of nucleic acid does not cause a corresponding increase in uric acid in the urine, although all the nitrogen of the nucleic acid is excreted. Other experimenters have obtained similar results. Apparently about half of the purine nitrogen thus administered is excreted in uric acid, but the other half as urea.

If uric acid formed in human metabolism cannot be destroyed, then part of the purines of nucleic acid taken in with the food in these experiments must have been disintegrated into something else than uric acid. That such a transformation of purines by an indirect route, avoiding uric acid, *may* take place must be admitted as possible, until either proved or disproved, neither of which has yet been done. There is evidence, however, that is not in favor of this hypothesis, and Siven[9] has found that *B. Coli* will disintegrate purines in culture fluids, which makes it possible that the purine of ingested nucleic acid which does not reappear in the urine as uric acid, may have been destroyed by intestinal bacteria. Divergent results in feeding experiments may be explained thus by differences in the character of the intestinal flora and the rate of absorption. Further, the studies in Müller's clinic on the metabolism of the nucleosides,[10] adenosin and guanosin, show that both in normal and gouty individuals the purines of these nucleosides are excreted as uric acid, which indicates that they are not disintegrated by some special route which avoids the formation of uric acid. Also in leukemia and pneumonia we find evidence that the purines liberated from the disintegrated nuclei are excreted as uric acid, and no evidence of other transformations. It is, indeed, improbable that one mammal should have a special method of destroying uric acid unknown in any other mammal, especially in view of the identity of other processes of purine metabolism all through the animal kingdom.

We may therefore state the case of uric acid in human metabolism to stand at present as follows:

(1) There is conclusive evidence that the human organism does not oxidize uric acid formed in metabolism into allantoin, as all other mammals except the anthropoids seem to do. (2) There is no conclusive evidence that man destroys uric acid by any other method, although it has not yet been positively established that he may not do so. (3) There is perhaps more reason to suspect that part of the purines of nucleic acid may be destroyed without passing through the stage of uric acid, but there is no direct evidence whatever that such a method of purine katabolism does exist. (4) It is highly probable, in consideration of what seems to be the best available evidence, that most of the purine of human food and practically all the purine from cell metabolism is converted into uric acid and excreted as such. Some of the food purines may be destroyed by bacteria in the intestines.

[8]Jour. Biol. Chem., 1913, xiv, 419.
[9]Arch. ges. Physiol., 1914, clvii, 582.
[10]Zeit. physiol. Chem., 1914 (91) 336.

# THE FERMENT-ANTIFERMENT BALANCE OF THE SERUM*

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AMONG the numerous chemical and physico-chemical systems of balanced reactions that occur in the animal organism few offer a more interesting field of investigation than that existing between the proteolytic serum ferments on the one hand and the serum antiferment on the other. Interesting not only to the physiologist in its influence on the normal metabolism but especially to the pathologist because of the fundamental importance which the whole domain of protein intoxication has assumed in the recent development of the study of pathological problems.

For the clear conception of the potential toxicity of the protein molecule we are in debt to the work of Vaughan in this country and to Pfeiffer, Friedberger, Kraus, Zunz and numerous other investigators in Europe, as a result of whose work we now know that the split products of proteins, especially the larger fragments, are toxic no matter what their source; that no well defined "antitoxin" is formed following injection of such split products, but that the protein fragments themselves, on further hydrolysis, become nontoxic. Under these circumstances we should expect that the presence of proteolytic ferments in the serum would lead to an immediate intoxication of the animal. To prevent such an untoward result the blood has been provided with an antiferment.

Our knowledge concerning both serum protease and antiprotease has been limited in the past, due possibly to the fact that effect rather than cause has been studied by most workers, while of the two factors in the balance, the antiferment has received the greater share of attention largely because of certain alterations in its titre which were observed clinically.

## Serum Antiferment.

Three theories have been formulated concerning the nature of the antiferment. It was regarded at first as a true antibody similar to those obtained when toxins are injected into an organism; the secretions from the leucocytes or the pancreas being considered the source of a constantly stimulating antigen. This position is, however, not only not physiological but the experimental evidence brought against it is so complete that it has been abandoned. The supposition was next advanced that the antiferment action was due to the accumulated split products of proteins in the serum which checked further enzyme activity. It was found, however, that the experimental evidence presented by Rosenthal in advancing this theory was incorrect. Among the first to suspect that the serum lipoids might have some relation to the antiferment property was Schwartz. Several serious objections were immediately advanced against this idea: the extracted lipoids appeared to be inactive; lipoid rich sera were not necessarily more strongly antitryptic than normal sera. Our interest in the subject was based on observations made during the course of studies concerning the

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mechanism of caseation in tuberculosis. In that process we determined that the lipoids, probably derived largely from the tubercle bacilli, completely inhibited tryptic digestion, thus accounting for the lack of autolysis in the diseased foci. When such lipoids were saturated, as with iodin, the inhibitory effect was lost In order to study the lipoids to greater advantage we saponified various preparations, in this manner greatly increasing the dispersion. It was found that the antiferment property was proportional to the degree of unsaturation of the soaps.

In the serum itself it had previously been observed that the lipoid solvents —ether, chloroform, etc.—removed or destroyed the antiferment, and Opie had noted that dispersion changes, such as are induced by acidifying the serum, rendered it inactive. Heating the serum to about 70° C. for 30 minutes has the same effect. On closer investigation we found that the extracted lipoids of the serum were actively antitryptic if their degree of dispersion was brought back to approximately its original state, as for instance by saponifying the lipoidal residue. We were able to demonstrate then that (1) the antiferment property of the serum depended upon the lipoidal constituents, whose activity depended on the degree of unsaturation and the degree of dispersion; (2) the antiferment was extractable in lipoid solvents, (3) the residue was actively antitryptic when the dispersion was again brought back to approximately the original state.

### The Serum Protease.

The nonspecific serum protease has been studied very little. Hedin had observed that ox serum contained a weak proteolytic ferment, associated with the globulin fraction of the serum protein. Delezenne and Pozerski had previously made the interesting observation that serum treated with chloroform became actively proteolytic when incubated, but found no explanation for the phenomenon; Von Dungern and Hirschfeld, too, had observed that serum treated with iodin underwent autolysis. Later, Opie considerably extended the studies commenced by Hedin.

All this work was of fundamental importance, but the facts determined remained isolated and without connection. As to the relation between the ferment and antiferment, Hedin rather considered the combination as a true proenzyme or zymogen, indeed typical for such a stage of the ferment, regarding the activation of the ferment merely as a process by means of which the antienzyme was destroyed.

On investigation we determined that the protease is present in all guinea-pig sera, usually in dogs and rabbits, rarely in human sera. It is usually inactivated when the serum is heated to 56° for 30 minutes, although occasional heating to 60° for 30 minutes will not inactivate the protease completely. Its activity is best demonstrable in a neutral or slightly acid reaction; it retains its activity unimpaired when dried, and for a considerable period of time when the fresh serum is placed in the ice chest. It is polyvalent in character, but bears no relation to the leucocytes.

### Serotoxin, Anaphylatoxin and the Mechanism of Anaphylatic Shock

If we now investigate a serum which under normal conditions contains considerable ferment, such as that of the guinea-pig, and determine the changes that occur when the antiferment is removed, several rather interesting phenomena

are observed. The serum becomes highly toxic for its own species. Thus one sample, incubated with chloroform for twenty-four hours became so toxic that 0.3 c.c. were sufficient to kill a medium size guinea-pig almost instantly. On further incubation the toxicity decreases, while a progressive increase in noncoagulable nitrogen can be observed during the course of the incubation.

The symptoms in the injected animals closely simulate anaphylatic shock. Following recovery from a sublethal dose there results a moderate increase in resistance to reinjection, similar in extent to that which Zinsser and Dwyer have observed following injection of anaphylatoxins.

It is well known that there has existed for several years considerable doubt as to the source of the toxic material of the so-called "anaphylatoxins." According to Friedberger and his school, the fresh serum digests the antigen, which is added in the form of bacteria, precipitates, corpuscles, etc., with a resulting splitting of the antigen to toxic split products. Opposed to this view we find arrayed the physical hypothesis which Ritz and Sachs, Doerr, Bordet and others have formulated. It was observed that quite inert substances, such as kaolin, barium sulphate, agar and starch would, when incubated with the serum, render the serum toxic; quite obviously split products, if responsible for the toxicity must be derived from the serum itself. Nor has it been clearly demonstrated that a splitting occurs when the bacteria are treated with fresh guinea-pig serum. Donati, for instance, found the bacteria intact as far as antigenic properties were concerned, while Neufeld and Dold noted that bacteria which did not undergo lysis by the serum were more efficacious than those which dissolved during anaphylatoxin formation.

In view of the rapid development of the toxicity of guinea-pig serum when its antiferment is removed by chloroform we quite naturally were justified in assuming that during typical anaphylatoxin formation adsorption changes occur by means of which the serum antiferment is adsorbed and the serum proteins themselves hydrolyzed, rather than the introduced antigen. From a purely physical viewpoint this is quite rational, for the lipoids in general and the fatty acids more particularly are easily adsorbable substances. Our investigation showed this hypothesis to be substantially correct, and it has been recently confirmed. We found that the antiferment was adsorbed by the bacteria; that the noncoagulable nitrogen increased, and that the bacteria, because of adsorption of antiferment, became more resistant to tryptic digestion.

If such conditions explained the toxicity of the anaphylatoxin, might it not be possible that a similar mechanism occurred during anaphylatic shock? In order to carry out these experiments we used dogs exclusively, because of the larger amounts of serum needed. We found that following the first or sensitizing intravenous injection of the antigen there were practically no serum changes as far as the ferments or antiferments are concerned. When, however, a reinjection is made after the animal is fully sensitized the following changes were noted immediately after the injection: The antiferment was markedly diminished; there was a striking increase in serum protease and lipase; an increase in noncoagulable nitrogen and amino nitrogen; a decrease in serum proteoses. The increase in amino acids might be interpreted as proof of the fact that hydrolysis of the antigen had occurred, as Zunz and György maintain, but under such circumstances we should expect that there would also be an increase in the

higher split products, such as the serum proteoses. This does not obtain. We are rather inclined to place the emphasis on the change between the ferment-antiferment balance which here greatly favors proteolysis. Under such circumstances it seems more probable that it is the serum protein itself which is hydrolyzed to toxic products and that the injected antigen initiates the process by causing the instantaneous mobilization of the nonspecific protease, together with changes in the colloidal dispersion whereby the serum lipoids become less active as antiferments.

### Concerning the Mechanism of the Abderhalden Reaction.

It is quite apparent from the preceding work that the serum itself, will, under proper conditions, hydrolyze and yield split products. Keeping this in mind, the repeated observations that a positive Abderhalden reaction can be obtained when quite inert substances are incubated with serum, such as kaolin, agar, etc., would naturally lead us to suspect that the same simple absorption phenomenon is at the basis of the Abderhalden Test. We do not believe that the specificity of the reaction in regard to protease action can longer be maintained in view of the adverse clinical findings reported during the past two years. Almost every febrile case will give a positive Abderhalden reaction against placenta at some time during its course, as Falls, among others, has shown. It has been noted, however, that during experimental immunization or sensitization a reaction is obtained which is seemingly specific. This we believe can be easily explained by the colloidal changes (precipitation—adsorption) which are induced in such sera when the antigen is added to them. The antiferment is diminished and in the local areas of deficiency so formed the serum proteases and ereptases can become active and digest the serum proteins with a resulting production of amino acids and a positive Abderhalden Test. We rather believe that the Abderhalden Reaction, while it has been of considerable value in calling attention to the importance of serum ferments, has really added unnecessary complication by the confusion of the ordinary immunity reactions with proteolytic cleavage supposed to be specific. As a result the normal polyvalent serum protease has been neglected.

### Serum Protease Following Injury by Burns, Hemolysins, Photodynamic Substances, etc.

Probably the only recent work has been that of Pfeiffer who has used glycyltryphthophan as an indicator of peptolytic activity. During the course of his studies he has noted that following injury, as for instance by burns, a great amount of ferment is thrown into the serum, which Pfeiffer considers as an evidence of cellular destruction, believing that the ferment is derived only from cells that are destroyed. He has noted the same increase after the injection of hemolysins, during photodynamic intoxication and also during anaphylatic shock. We do not believe that it is necessary to assume total destruction of cells before ferments are liberated, but rather that such a mobilization can occur from an injury which need not end in total destruction of the cell. In other words, the mobilization of the ferments can be regarded to some extent as a protective cellular reaction rather than as an evidence of cellular destruction.

### Changes During Lobar Pneumonia.

This seems to be made evident by the conditions that are found to prevail during the course of a typical lobar pneumonia. It had been observed previously that a rapid increase in the serum antiferment occurs during the course of the early stages of the disease with a decline at or just after the crisis. In a study of a number of cases we have noted that at the time of the crisis a well defined increase in serum protease occurs which again disappears as soon as the crisis is passed. We can regard the serum changes either as a reflection of the processes taking place in the involved area, or as primary changes which influence the pathological processes. Considering the intimate relation known to exist between the inception of autolysis in the involved lung and the recovery of the patient it would seem reasonable that these two observed factors—a lowering of the antiferment titre and the increase in the amount of protease—are of importance in initiating the autolytic process in the lung, and thereby the onset of the crisis. In this explanation we of course assume that the source of the toxic substances are not to be sought solely in the pneumococcus protein, but that the pneumonic exudate itself, consisting of a tremendous amount of fibrin and leucocytic debris, a foreign mass in so far as the lung is concerned, represents a matrix of potentially toxic substances. As long as the inhibitory factors are in the ascendancy the digestion of this material must proceed slowly, so that only the higher toxic split products are absorbed. As soon as the inhibitory factors are overcome, however, active autolysis can begin, the lower split products only will be absorbed and recovery can take place. Falls has recently demonstrated an increase in proteolytic serum ferments at the time of the crisis by means of the usual Abderhalden technique. Such a ferment increase might be interpreted as having its origin in the leucocytes of the involved lung tissue as Falls states, rather than being considered a reaction product of the cells as a whole. Were this the case we should expect that the ferment would continue to be present for a considerable time after the crisis, when autolysis is rapidly clearing the lung tissue. This, however, is not found, for after the crisis the protease almost immediately drops back to its original titre. Falls has not been able to find any relation between the leucocyte curve and the protease content of the serum, nor have we noted any connection. It would therefore seem reasonable to suppose that the serum protease does not take origin from the leucocytes. Nor is its source the pancreas, for when the organ is excised, the animal responds with a mobilization of protease on intoxication just as it would normally.

### Bacteriotherapy.

Our interest centered naturally about studies of the ferments following bacterial injections. As a result of the work that has originated through the study of the Abderhalden reaction, numerous efforts have been made to obtain specific ferments against bacteria, with results quite at variance. It is of course well known that bacteria are resistant, both when living and after being killed in various ways, to the most powerful proteolytic ferments, a resistance due most probably, we are inclined to believe, to the fact that the limiting membrane of the organism is largely lipoidal in character. We have found that various dried organisms are resistant to digestion almost in proportion to the amount of unsaturated lipoids contained.

While therefore no effect of the strong polyvalent tryptic ferments have been observed, Abderhalden and various workers have endeavored to show that specific ferments might be obtained that would digest the bacteria. The evidence for this assumption is quite contradictory, and rests, we believe, on the ordinary immunity reactions. The whole subject is important from the therapeutic point of view, especially because of its bearing on vaccines and bacteriotherapy in general.

As a result of our studies we have observed that the intravenous injection of dried organisms is followed by a very rapid mobilization of serum protease and lipase, the increase being proportional in general to the toxicity of the organism, and its resistance to tryptic digestion. Thus following an injection of 10 mg. of dried typhoid bacteria in a dog the proteolytic activity of the serum increased from an original titre of 0.1 mg. (the amount of noncoagulable nitrogen formed from 1 c.c. of serum under chloroform in about 18 hours) to 0.78 mg., five hours after the injection; the lipase titre increasing at the same time from about 1 c.c. N/100 NaOH (the acidity produced from 1 c.c. ethyl butyrate by 1 c.c. serum in 4 hours) to 6.5 c.c. N/100 NaOH. With tubercle bacilli on the other hand, which are resistant to digestion, practically no changes were noted in the serum ferments.

It is a well recognized fact, admitted even by Wright, that the therapeutic results following the injection of bacteria (vaccines) are not to be explained wholly on a specific basis, certain facts indicating that nonspecific benefits result from bacteriotherapy. The possibility that the explanation for this effect is to be sought in the mobilization of nonspecific ferments, such as we have demonstrated following bacterial injection, must be kept in mind.

This subject has assumed a more than casual interest in view of the numerous reports of the successful use of vaccines administered intravenously during the course of typhoid fever. Inasmuch as antibodies are being formed with considerable constancy during the disease under the usual conditions, there could, theoretically, be no object in seeking to stimulate a function of the cells already producing these substances to their full capacity. And the recent reports of almost immediate recovery following the intravenous injections of vaccines have emphasized the fact that following such injections there are practically no changes in the antibody concentration. This would seem to be in line with the understanding reached in late years that recovery in typhoid fever cannot be explained wholly on the basis of the production of the ordinary antibodies, for the patient may indeed reach a high antibody concentration long before the disease process has been checked. The observation of Kraus, among others, that the defervescence occurs as well after an injection of colon vaccine in typhoid fever, and of Ishawara, who aborted paratyphoid infections with typhoid vaccines, leaves no room for doubt that the idea of specificity is to be excluded in the mechanism and that an explanation must be sought along other lines.

In this connection it should be pointed out that there are certain objectionable features to the bacteriotherapy as used in typhoid fever, objections inherent in the toxicity of the organisms and only partially overcome by the treatment with serum such as used in the preparation of the Besredka vaccine. These concern chiefly the effect on the circulatory apparatus, with occasional evidences of a grave collapse, and the increase in peristalsis.

If we regard the therapy as one designed to stimulate a mobilization of non-specific ferments it might be possible to elicit such changes without the employment of an agent itself toxic. To this end we have studied the effect of the intravenous injection of the various split products of proteins, using several proteose and peptone solutions. As Jobling and Strause and Zunz have shown, the secondary proteoses are much less toxic than the primary, the use of such solutions might be of value if the stimulation is sufficient. Lüdke has worked along a similar line and reports very favorable results when solutions of deutero-albumoses are injected intravenously during the course of typhoid fever.

### The Effect of a Chill on the Antiferment.

The injection of the vaccines as well as the deuteroalbumose solutions is followed clinically by a marked chill, and the serum examination usually shows a well defined reduction in antiferment titre immediately after the chill. Experimentally a similar phenomenon is noted when guinea-pigs, for instance, are chilled for a period of about one-half hour. Thus in one animal the antiferment titre fell from 59% to 0.0% per 0.075 c.c. of serum, in another from 75% to 59%. Inasmuch as the antiferment consists of highly dispersed lipoids, it seems reasonable that during the greatly increased metabolic demands incident to the chilling of the animals, the lipoids would be used as available material. We therefore feel justified in ascribing the lowering of the titre following the vaccine injection to a similar cause. This fact in conjunction with the possible increase in serum protease would of course greatly facilitate proteolytic processes.

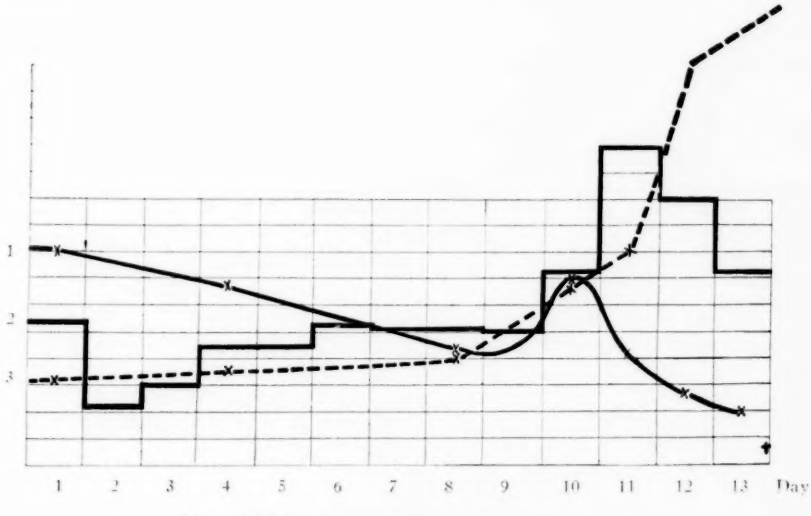
### The Cause of Death from Inanition.

The lowering of the antiferment titre due to a similar metabolic demand and involving an interesting form of true auto-intoxication, is that which occurs during starvation. It is of course a well known phenomenon that a large increase in nitrogen excretion occurs just before death in starving animals,—the so-called premortal rise,—while the animals themselves, during the course of the experiment, present definite evidences of intoxication, to such an extent that Schulz has advanced the idea that during starvation the body metabolism is so altered that periods of intoxication occur at intervals, culminating in the death of the animal from such a cause. Schulz's views are contrary to those of Voit, who connects the death of the animal with the exhaustion of the fat depots of the body. In studies which we have made we have determined the following facts: During the course of the experiment a definite and progressive lowering of the antiferment titre occurs, a minimum being reached just before the premortal excretion of nitrogen. At this time the noncoagulable nitrogen of the serum increases very markedly and the serum protease overbalances the inhibitory effect. A typical protein intoxication occurs, with an increase in antiferment following as a reaction. If sufficient to check the process the animal may recover and live over an additional period of several days; if not, death ensues rather promptly. The death is therefore not of necessity due to a lack of available energy material, but to an intoxication due to protein split products formed when the antiferment has been reduced to such an extent that the ferment overbalances it. If the antiferment is artificially increased the animal may be tided over such periods of intoxication, just as we have shown that the antiferment may afford some protection against anaphylatic shock.

An illustrative experiment is shown in the accompanying chart.

Curve 1 represents the antiferment titre in per cent of inhibition per 0.075 c.c. serum. Curve 2 represents the daily total nitrogen excretion in tenths grams. Curve 3 represents the total noncoagulable nitrogen per c.c. of serum in tenths milligrams.

It will be observed that the premortal rise in nitrogen excretion began in this rabbit on the tenth day. The changes in the ferment-antiferment balance had occurred the day previously, i. e., on the ninth day, when the antiferment titre reached its lowest level. As a result an intoxication occurred, evidenced by the progressive increase in noncoagulable nitrogen and the increase in antiferment for a short period. The animal died on the thirteenth day of the experiment.




THE THERAPEUTIC EFFECT OF IODIN.

The lowering of the antiferment titre and the resulting aid to proteolytic processes need not of necessity lead to disastrous effects, indeed it seems that it had been the basis of the mechanism by means of which iodin has been of great value therapeutically.

In studying a series of cases placed at our disposal through the courtesy of Dr. Fordyce and his associates, we have noticed that under a course of iodides the antiferment titre is quite constantly diminished. Whenever symptoms of iodism occurred, the titre again increased to its former or greater value. Experimentally it has been shown previously that iodides and iodin increase the autolysis of macerated organs, but when injected into animals the effect on the antiferment has as a rule been an increase. This latter fact is most probably due to the large doses used and to the fact that practically all experimental animals have a low titre to begin with as compared to human sera, so that changes are much less pronounced.

The manner in which the iodin lowers the antiferment titre is we believe rather simple. The antiferment property, depending on the unsaturated bonds of the lipoids, is diminished by any agent which tends to decrease the unsaturation of these bodies. Iodin and iodides given over a period of time gradually are taken up by the lipoids and saturate these valences with a resulting les-

sening of the antiferment property. Whatever proteolytic ferments are then present will of course have a greater field of action and necrotic tissue especially will undergo autolysis and disappear. This explanation offers a reasonable basis for an empiric therapy which is of undoubted value in the removal of necrotic material; in the exposure of diseased foci in necrotic masses to the effect of specific therapeutic agents; and possibly in the treatment of infectious diseases when greater proteolytic activity is to be obtained.

### The Increase in Antiferment.

That an increase in antiferment would be of value in preventing the formation of protein split products and thereby act as a protective agent is beyond question. There seems to be evidence however, that an increase in the antiferment may perceptibly alter the metabolism of the organism, as for instance in bringing about the condition of hibernation. Theoretically it should be possible to increase both the intracellular as well as the serum antiferment to such an extent that protein cleavage of any kind would be held in abeyance.

During the course of our work we have noticed that even in dogs the antiferment titre seems much lower during the summer than the winter, the decrease in some instances amounting to fully fifty per cent. Probably the work of Mayer and Schaeffer is suggestive in this connection. By means of careful quanitative studies they noted that there was not only an increase in the relative amount of lipoids of the serum and tissues during hibernation but the iodin value of the lipoids was greatly increased, indicating an augmented antiferment power. Whether this bears some relation to the peculiar glandular enlargements noted during hibernation has not been determined. The subject is one of several in which the direct influence of the antiferment seems apparent. The field is so broad and the applications so many that we have simply endeavored to indicate a few lines along which the relative changes between ferment and antiferment have seemed to us to play a part in the mechanism of pathological and physiological processes.

A complete review of the literature is found in a series of papers published in the *Journal of Experimental Medicine*.

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## EXPERIMENTAL AND CLINICAL STUDIES ON MENTAL DEFECTIVES, I.

### A Practical System of Diagnosis and Study Based on the Principle of Growth-Development as the Expression of Constitutional Character or Defect.

By Amos W. Peters, Ph.D., with the assistance of Caroline D. Blackburn,
Philadelphia, Penn.

THE view of the pathology of the feeble-minded which is expressed in the above title is the outgrowth of several years of combined laboratory and clinical study of such cases. The technic here described is designed for the examination and study of the mental defective from the physio-pathological as

well as the psycho-pathological standpoint. I believe that the evidence of studies made by this technic shows that with mental defectives including the feeble-minded we are studying primarily errors of physical growth and development whose essential nature is not simply neural but extends in some degree, and in many cases most pronouncedly, to any or all other systems of organs. This practical generality of pathological condition we may justly ascribe to intimate hormonal or neural correlation or both. In the majority of cases these deviations from the normal course are constitutional, i. e., they are inherent in the character of the germ cells, they begin with the parentage, are continued and magnified during the period of gestation, and are deeply impressed in the physical constitution of the individual so that abnormal growth and development characterizes such individual not only during gestation but continuously after birth. The acquired cases differ from the others only in the fact that the *incidence* of the disturbance of their growth-development has occurred at a later period in the cycle of development. The fundamental fact even in these cases is still the perversion of the normal course of growth and development of the physique.

The feeble-minded, therefore, stand before us as a biological, a pathological phenomenon, the physio-pathological study of which can be differentiated into a physiological and a biochemical subdivision. It should be noted that the pursuit of this problem by any one physiological or pathological method exclusive of the others is fatal to the success of that one method itself. As subsequent publication of our study of these cases will show, this fact is due to the complexity of these pathological conditions, which greatly exceeds that of the current conception of the simple omission of a something from their neural development. Having begun with an effort to further the solution of the pathological problem of the feeble-minded by the immediate application of the biochemical method, it gradually became evident that for intelligent orientation and interpretation this method stood in need of a generalized viewpoint to guide its attacks. Experience demonstrated that such study should be preceded or at least accompanied by a preliminary introductory examination of an anatomico-physiological nature. It was thus found necessary to evaluate the physique physiologically and pathologically, upon which experiment by the biochemical method was to follow. We have therefore described our technic in its logical order, thus deferring the biochemical parts to subsequent papers. For the purpose of this preliminary orientation the system of procedures below described was evolved from the practical examination and study of sufficiently numerous cases and this method is now used as an introductory and diagnostic routine for subsequent more intensive studies as shown below in the general plan. Its utility and application is by no means confined to a first examination. The development of this system has placed the writer in the possession of the results so obtained on fifty miscellaneous cases comprising eighty-two examinations which include both normal and pathological individuals. An interesting part of this material consists of several family groups in which are comprised both psychologically normal and psychopathic members of the same family. These results will be subsequently reported.

The utilities of the following orderly system of examination and study may

be summarized as follows. *First*, stands the immediate diagnostic value of the results thus obtained. *Second*, the observation and measurement of growth-developmental changes as they occur in the natural course of physiological development of both defective and of normal subjects and the resulting possibility of accurate comparison with the growth-development of normal individuals. *Third*, the measurement of growth-developmental changes as a measure of the results obtained by any given method of care and treatment, whether the conditions be physiological, pathological or experimental. *Fourth*, the study of the inheritance of the characters involved, or shown by a comparison of the results obtained on family groups.

In this connection we may record our experience, that because the technic here described touches the personality of the subject in such manifold ways, a competent and experienced examiner will successfully diagnose from 75 to 100 per cent of unselected mental defectives independently of the customary psychological examinations. This is not to be taken as an argument or justification for the omission of the latter, for our plan of investigation definitely provides for an examination of the mental ability of the subject. However, the above success which we have repeatedly observed does show how intimate and evident the correlation between physiological and psychological conditions is in these cases.

It should be noted that the same technic is intended to serve the important purpose of making a parallel survey of mentally normal subjects not only for comparison with the defective but also for the study in the human subject of normal growth and development itself. The importance of such surveys of normal individuals for both scientific and practical purposes should not be underestimated. The collective data on well selected normal material are too few in the literature, the results that might thus be obtained are of evident importance, and the experience to the examiner of noting certain contrasts in the results obtained on normal and defective subjects, are considerations that should induce one to make use of every opportunity that offers for obtaining data on any physically peculiar but mentally normal person whether child or adult.

We are confronted at the outset with the practical question as to which examination we should make first, the physio-pathological or the psycho-pathological. Customary practice thus far scarcely takes cognizance of the practical significance of anything beyond the psychological examination. Physical examinations it is true are made as an almost meaningless routine, for they are not correlated with the mental findings, are not incorporated as related integrals into the ensemble of a complete examination, and they are too often made only from the physician's customary standpoint of the temporary health of the subject and thus completely fail to seize those data which pertain to the growth-developmental defects which are the most fundamentally important facts in the pathology of the case. In our opinion the systematic survey should begin with the physiological examination rather than the psychological. Experience will teach the examiner that the present physique of the subject, his physio-pathological history, the history of his growth and development and the ascertainable facts of his heredity provide a logical background for the psychological findings. The direction of logical explanation is from the physiological condition as a causa-

tive basis to the psychological as an intelligible effect and not the reverse, especially in the case of mental defectives, regardless of what opinion one may hold for certain other psychiatrical cases or conditions. To interpret the psychological findings or in the present state of our knowledge even to make an attempt to explain them, the underlying physio-pathological conditions must be recognized to be the determining substratum. The reverse procedure may possibly some day become practicable when our knowledge shall have increased far beyond its present bounds. To the practical examiner who comes in contact with such cases as will be subsequently described in these papers and who accustoms himself to place in juxtaposition both physiological and psychological findings the above arguments are superfluous. Our purpose is rather to emphasize the necessity of actually making the right kind of physio-pathological examination and especially of practically recognizing the pathogenetic relation between the physical and the mental findings.

At this point we desire to guard against certain misconceptions which are probably due to use of the term "examination." The investigation of a subject as here planned is rather a study, the preliminary and introductory parts of which may be made at a single initial conference occupying from two to three hours or more depending upon the findings. The kind of examination here described involves careful observation, and especially experimental physiological testing with which hasty and routine procedures are wholly incompatible. The examiner needs an assistant both for the procedures themselves and for recording from dictation the measurements and observations or two examiners can profitably work together. The writer working under institution conditions permits two women assistants to do as much of the preliminary examination as they are trained for and accustomed to do but makes it a rule to survey each new case carefully himself at the close of the introductory examination and then dictates his own observations as personal "addenda" to the record already made. This saves the examiner's time without depriving him of an increasing and very desirable first-hand experience. The form of record should be so flexible and adjustable as to permit extended description where the conditions indicate its value. The worst form of record is that which provides a fixed and usually small space for the same heading for all cases. This form encourages routine expression and omission. It will happen that a heading in some cases will require extended description, in others only the word "negative" or "normal." We therefore adopt the plan of having a printed or typewritten outline before us as a guide in which each point to be noted is given an unchangeable number by which it is represented in the written record thus permitting the space for each heading to be adjusted to the greater or lesser extent of the findings in each case. Great care should be taken to preserve in systematic way the original records which are made in the presence of the case and to distinguish between these and any copies or elaborations subsequently made. The trained laboratory worker, of course, always observes this distinction and rigidly refrains from substituting a "copied" record which is "nicer" or "better" for the original made in the presence of the facts themselves. The observer should if necessary train himself away from the duplication of labor and the experimental error involved in copying first records of observations for

the purpose of improving them. The disorder thus sought to be remedied must not be permitted in the first instance. All records must bear prima facie evidence as to who made the observations and when they were made.

It should be emphasized that the utility of the present plan of examination and study is by no means confined to a first or preliminary investigation. A study of the progressive growth-developmental changes of a young person or of the progress of certain pathological changes can be made by repeating at proper intervals selected portions of the plan of measurements and of observations and tests. It is surprising for what short intervals exact measurements can demonstrate growth in a rapidly developing young subject as some repeated measurements recorded by this method show. An accurate record of such measurements and observations on development taken on the same individuals of both normal and of mentally defective types would be highly interesting and detailed data on the history of the same individual are exceedingly rare if not entirely absent from the literature. On the other hand there are considerations which make a certain amount of repetition of measurements when the subject is not perceptibly changing of importance. Such repetitions made by the same and by different examiners give us the data for estimating the limits of variability of the method itself either in the hands of the same or of several different examiners. It will also soon become apparent to the practical worker that some items in the scheme of measurements are capable of much more exact repetition than others and he should have some conception of the amount of the variability for each measurement. To this subject we shall return later in the discussion of some of the results obtained.

We now come to the practical question as to what should be included in an adequate scheme of examination and diagnosis of the mental defective which scheme should not stop at this point but also furnish the basis for further study and research. The content of such a scheme will be much influenced by two factors one of which is the author's views on the possible pathogenesis of such cases and the other is the present state of our knowledge or better, the present degree of development of the method and technic of scientific investigation. After having studied the pathology of these cases for a number of years and having made what must of course be only a personal survey of current scientific method that is available or that can be applied to the problem, the writer ventures to propose for consideration the following subdivisions of such a scheme:

## GENERAL PLAN FOR THE STUDY, DIAGNOSIS AND INVESTIGATION OF MENTAL DEFECTIVES

A. Anthropometric measurements.

B. Physio-pathological observations and tests, including data on abnormalities of growth-development.

C. Physiological and pathological history of the individual.

D. Family history and especially data pertaining to the mother during the period of gestation.

E. Mental, and especially intelligence, tests and studies of the individual both independently and in the light of the preceding data.

F. Experimental physiological and biochemical evaluation of the pathology of the individual, especially studies on the metabolism and blood.

G. Experimental care-taking of feeble-minded individuals or of small groups for the *application* of all the available scientific data above obtained, or obtainable in scientific literature, to the *physical improvement* of these subjects, including especially their diet and nutrition.

H. Anatomical, histological and biochemical studies on the organs and tissues of the individual, especially on the nervous and the glandular systems, inclusive of glands of internal secretion.

Armed with a foundation of pathological knowledge we could now add the logically following topics of prevention, therapeusis if any, personal care and management of these cases, and finally the most scientific solution of the sociological problem of the mentally defective.

## OUTLINE FOR THE EXAMINATION AND STUDY OF MENTAL DEFECTIVES

### Division A. List of Anthropometric Dimensions.

*Group I: Some General Dimensions. See Notes Nos. 2-14.*

1. Age = A. 2. Weight = W. 3. Total height = H. 4. Arm span = S. 5. Height to lower margin of symphysis pubis = Sy. 6. Height to navel = Na. 7. Height to iliac crest, Right, Left = I.

*Group II: Thoracic Dimensions. See Notes Nos. 2-14.*

8. Smallest neck circumference. 9. Total basal profile = Bf. 10. Sections of basal profile, Bf1, Bf2, Bf3. 10a. Drawing of basal profile. 11. Basal line = (Friedenthal's a) = B. 12. Transverse shoulder line = (Friedenthal's b). 13. Transverse thoracic diameter at level of axillae, i. e., at 4th costal cartilage. 14. Dorso-ventral thoracic diameter at level of axillae, i. e., at 4th costal cartilage. 15. Dorso-ventral thoracic diameter over nipples. 16. Thoracic circumference at level of axillae on inspiration. 17. Thoracic circumference at level of axillae on expiration. 18. Thoracic circumference over nipples. 19. Suprasternal nipple line, Right, Left. 20. Transverse straight line between nipples. 21. Length of vertical breast contour. 22. Vertical distance of nipple parallel from parallel of substernal notch.

*Group III: Abdominal Dimensions. See Notes Nos. 2-14.*

23. Smallest circumference of waist. 24. Abdominal circumference at iliac level. 25. Dorso-ventral abdominal diameter at iliac level. 26. Transverse abdominal diameter at iliac level. 27. Transverse pelvic line at level of symphysis pubis = (Friedenthal's d).

*Group IV: Appendicular Dimensions. See Notes Nos. 2-14.*

28. Circumference of thigh at level of crotch, Right, Left. 29. Circumference of arm at level of axillae, Right, Left. 30. Right upper extremity—upper arm, forearm, hand extended, (inc. carpus). 31. Right hand—middle metacarpal, phalanges I, II, III. 32. Right little finger—phalanges I, II, III. 33. Left upper extremity—upper arm, forearm, hand extended, (inc. carpus). 34. Left hand—middle metacarpal phalanges I, II, III. 35. Left little finger—phalanges I, II, III.

*Group V: Cephalo-Spinal Dimensions. See Notes Nos. 2-14.*

36. Cranial length. 37. Cranial width. 38. Cranial height. 39. Cranial circumference. 40. Frontal arch. 41. Frontal radius. 42. Height of head.

DIVISION B. GENERAL ANATOMICO-PHYSIOLOGICAL AND NEUROLOGICAL OBSERVATIONS AND TESTS.

*Group VI: Skeleton, Figure, Posture, Locomotion. See Note No. 15.*

51. Proportions, observable. 52. Skeleton, general and extremities—bones, large, small, medium, normal. Extremities, normal or curved. 53. Deformities. Description of anatomical condition. 54. Cephalic skeleton. Size, conformation, sutures. 55. Thoracic skeleton. Pathological types. 56. Abdominal protrusion. 57. Peculiarities in posture. 58. Gait. 59. Locomotion to point, blindfolded. 60. Ability to heel and toe a line.

*Group VII: Skin, Hair, Nails, Sweat Glands, Fat. See Note No. 15.*

61. Color and surface of skin. 62. Color and texture of hair, comparative of scalp, axillae, genital region, other surfaces. 63. Growth and distribution of hair. Abdominal hair line. 64. Nails. 65. Sweat glands. 66. Fat, quantity and distribution.

*Group VIII: Mouth, Nose, Throat, Ears, Eyes. See Note No. 15.*

67. Conformation, especially of arch. 68. Teeth. 69. Tongue and its glands. 70. Tonsils. 71. Pharynx and adenoids. 72. Ears. 73. Eyes.

*Group IX: Genitals and Superficial Glands, Pelvis. See Note No. 15.*

74. Developmental stage, size, glandular conditions. 75. Deformities or abnormalities in secondary sexual organs. 76. Anatomical internal genito-urinary conditions. 77. Genito-urinary functional activity. 78. Anatomical rectal conditions, and rectal functional activity. 79. Inguinal. 80. Mamillary-axillary. 81. Cervical. 82. Thyroid.

*Group X: Internal Organs—Cardio-vascular, Pulmonary, Abdominal. See Note No. 15.*

83. Vaso-motor conditions as observed in the skin. 84. Position of apex beat. 85. Character of sounds by stethoscope. 86. Pulse: Rate difference lying and standing, regularity or intermittence, force. 87. Blood pressure, lying, standing. 88. Respiration: Type, number. 89. Spirometer. 90. Abdominal conditions.

*Group XI: Neuro-Muscular Organs and Reflexes. See Note No. 16.*

91. Automatism. 92. Dynamometer. 93. Tremor of spread fingers. 94. Pupillary and conjunctival. 95. Knee jerk. 96. Plantar. 97. Babinski. 98. Ankle. 99. Epigastric. 100. Abdominal. 101. Sensitivity to needle. 102. Sensory defects. 103. Speech defects.

*Group XII: Mental, Especially Intelligence Tests. See Notes Nos. 2-14.*

*Group XIII. Blood: Cytology, Immunology, Biochemistry.*

110. Absolute blood count. 111. Differential blood count. 112. Hemoglobin. 113. Coagulation time. 114. Wassermann reaction. 115. Tuberculin reaction.

*Group XIV. Nutrition and Metabolism: Urine, Nitrogen, Calcium, Phosphorus, Chlorine, Sugar, Respiratory, Exchanges.*

120. Quantity, color, specific gravity of 24-hour urine. 121. Quantitative acidity of 24-hour specimen. 122. Albumen reaction of 24-hour specimen. 123. Sugar reaction of 24-hour specimen. 124. Quantitative calcium oxide of 24-hour specimen. 125. Quantitative phosphoric acid of 24-hour specimen. 126. Quantitative chlorine of 24-hour specimen. 127. Urinary sediment, inorganic, of 24-hour specimen. 128. Urinary sediment, organic, of 24-hour specimen.

NOTES ON TECHNIC AND REFERENCES.

It is evident that the qualifications of training and experience that *can* be applied in the above plan of examination and study ranges from that of the instructed laboratory assistant to that of the medically skilled and experienced professional person. An intelligent and educated person whose interests lie in this direction can learn to do nearly all of it in a satisfactory way. This statement applies to the ascertainment of facts but by no means to their interpretation and utilization. The scientific relations of many of these topics and their pathological significance must be left for illustration and discussion in the reports of cases so studied and which will be subsequently published. It would obviously require a booklet rather than a paper to enter into the details of the above technic. We shall therefore refer to the following sources of information which have been selected with special reference to the assistance they can give in the use of the above outline. This list does not constitute a bibliography of the topics involved but it is a sufficiently comprehensive guide to the necessary information regarding methods of procedure, instruments and apparatus required, as well as a further index to the literature.

*On the general topic of growth and development:*

(1) Friedenthal, Hans: Allgemeine und spezielle Physiologie des Menschenwachstums. Berlin, Springer, 1914. Pp. X + 161.

Contains a good bibliography on human growth.

*On Groups I to V, Anthropometry, and Group XII, Mental, Especially Intelligence Tests:*

(2) Report of Anthropometric Investigations, British Isles. Reprinted with additional illustrations by permission of the Council from the Report of the British Association (Dublin Meeting) 1908. Pp. 351. ff.

(3) Montessori, Maria: Pedagogical Anthropology. New York, Fred. A. Stokes Co., 1913. Pp. XI + 508.

(4) Hastings, Wm. W.: Manual for Physical Measurements. 1902. Pp. XVIII + 112.

Contains anthropometric tables for each age and sex from 5-25 years, also vitality coefficients.

(5) Pyle, William H.: The Examination of School Children. A Manual of Directions and Forms. New York, Macmillan Co., 1913. Pp. 67.

(6) Yerkes, Robert M.; Bridges, James W.; Hardwick, Rose S.: A Point Scale for Measuring Mental Ability. Baltimore, Warwick & York, Inc., 1915. Pp. 218.

(7) Haines, Thomas H.: Point Scale Ratings of Delinquent Boys and Girls. From Juvenile Research Bureau, Columbus, Ohio. Psychological Review. Vol. 22, No. 2, pp. 104-109. March, 1915.

(8) Haines, Thomas H.: Diagnostic Values of Some Performance Tests. Bureau of Juvenile Research, Columbus, Ohio. Psychological Review, Vol. 22, No. 4, pp. 299-305. July, 1915.

(9) Goddard, Henry H.: Standard Method for Giving the Binet Test. Reprint from The Training School Bulletin, Vol. 10, No. 2, pp. 23-30. April, 1913.

(10) Healy, William: The Individual Delinquent. A text-book of diagnosis and prognosis for all concerned in understanding offenders. Boston, Sittle, 1915. Pp. XVI + 830.

(11) Healy, William, and Fernald, G. M.: Tests for practical mental classification. Lancaster, Penn., Review Pub. Co., 1911. Pp. VII + 53.

(12) Whipple, Guy M.: Manual of Mental and Physical Tests. Part I: Simpler Processes. Part II: Complex Processes. Baltimore, Warwick & York, Inc., 1915.

Part II, p. 324, presents a very well selected list of references on Serial Graded Tests for Developmental Diagnosis, by means of which the reader can orient himself on this topic.

(13) Thorndike, Edward L.: An Introduction to the Theory of Mental and So-

cial Measurements. 2nd ed. Published by Teachers College, Columbia University, New York, 1913. Pp. XI + 277.

(14) Stern, W.: The Psychological Methods of Testing Intelligence. Translated by Guy M. Whipple. Baltimore, Warwick & York, Inc., 1915.

*On Groups VI to X:*

(15) Eisendrath, Daniel L.: A Text-Book of Clinical Anatomy. 2nd ed. Philadelphia, W. B. Saunders Co., 1907. Pp. 535.

*On Group XI:*

(16) Hunt, Robert L. Diagnostic Symptoms in Nervous Diseases. Philadelphia, W. B. Saunders Co., 1914. Pp. 229.

*On Groups XIII and XIV:*

(17) The preceding parts of the above Outline, i. e., Groups I to XII pertain approximately to subheads A to E of the General Plan. The material of Groups XIII and XIV belongs more properly under Subhead F, which is essentially a research topic. Here each competent worker will want to make his own selection or invention of method adapted to his special purpose. For routine purposes the standard works on diagnostic technic will suffice.

(18) For such measurements as are taken standing, a certain uniform normal standing position must be adopted, e. g., heels in contact, body erect as is natural to the individual and not a straight pose. In measuring certain dimensions the distinction should be observed between distances measured on or across the body surfaces as contours or profiles and those of the nature of diameters and to be measured as straight lines between designated points or their projection in space.

(19) The Arm Span, (No. 4) should be taken as the distance measured on a straight horizontal line between the extreme points of the two middle fingers when the arms are extended at right angles to the trunk. Note that it is not correctly or accurately measured across the surface of the chest.

(20) The Total Basal Profile Bf, (No. 9) is measured on the anterior surface of the trunk from the suprasternal notch to the lower surface of the symphysis pubis. It is not commonly a straight line. Normal standing position.

(21) Section Bf1 of the basal profile, (No. 10) extends from suprasternal notch to the substernal notch, Bf2 from latter to navel, Bf3 from navel to lower margin of symphysis pubis. Normal standing position.

(22) Drawing of basal profile, (No. 10a) should be made to scale for the three sections and should correctly show the natural curvatures or angles as seen from a side view taken in normal standing position.

(23) The Basal Line B, (No. 11) should be taken as the distance measured on a straight vertical line from the level of the suprasternal notch to the level of the lower margin of the symphysis pubis. It is not a contour or profile line. Normal standing position.

(24) The suprasternal nipple line is measured in a straight line from the suprasternal notch to the right and left nipples respectively, regardless of sex or in any case of what the position of the nipples may be.

## Summary.

(1) The pathology of mental defectives including especially the feeble-minded is based on the principle that their condition, both physio-pathological and psycho-pathological is due to physical abnormalities of growth and development which affect not only the neural but also other systems of organs by reason of intimate hormonal or neural correlation or both. In the majority of cases these begin with the parentage, are continued and magnified during the period of gestation, and are deeply impressed in the physical constitution of the individual so that abnormal growth and development characterizes such individual not only during gestation but continuously after birth. In acquired defect the incidence of the deviation from the normal occurs at a later period in the cycle of development.

(2) An outline of a plan, based on the principle of growth-development, for the examination, diagnosis and further study of mental defectives, has been presented. This outline places emphasis on the physio-pathological factors as well as on the psycho-pathological and the facts thus ascertained constitute the logical basis for further intensive study of the defective individual by physiological and biochemical methods. —*Training School, Vineland, N. J.*

# LABORATORY METHODS

## A Method of Sterilizing Sputum Before Examination*

By Don M. Griswold, M.D., Detroit, Mich.

THE question of safety for persons handling tuberculous sputum in routine examination is one that from time to time receives some attention.

Between the extremes of wearing rubber gloves and a surgical operating gown and an utter indifference for personal hygiene and safety lies some rational procedure.

Many laboratories, both municipal and private, refuse to accept specimens in leaking containers. The safety of those engaged in this work demands this protection. Some laboratories send out sputum bottles containing a half ounce of a weak carbolic solution. This inhibits the reproduction of the accompanying organisms and leaves the field less confusing when searching for the tubercle bacilli.

The danger, however, is often on the outside of the bottle or carton, as well as on the inside.

The skillful manipulator will seldom become contaminated with the contents of the bottle, but the bottle or carton must always be handled. Thus it would seem important that if an effort is to be made to protect laboratory workers the whole outfit should be sterilized.

It has been the practice of the laboratory of the Detroit Board of Health to autoclave all sputum bottles after the contents have been examined, then send them to the dump. It was desired to study the effect of this treatment upon the sputum.

First it was found that almost regardless of the physical characteristics of the sputum before autoclaving, after this treatment the sputum was divided into two distinct layers. One of these is thin and watery and probably represents the saliva which was in the bottle. The other resembles soft boiled white of egg. It is sometimes discolored and may be of a greenish or brownish tinge. This is probably coagulated albumen from the sputum. As this is coagulated and falls to the bottom it engulfs and drags with it many of the bacteria contained in the sputum.

When this coagulated material is smeared it will be found that a comparatively even smear can be made very quickly. It is about the consistency of butter.

In a series of two hundred sputa examined first in the usual way, and then after autoclaving, the following results were obtained:

1. All sputa found positive in the usual way were found positive after autoclaving.

2. Among the sputa found negative (150) in the usual way, three showed tubercle bacilli after autoclaving.

The staining characteristic of the tubercle bacillus is not altered so far as we have found. The organism retains the carbolfuchsin in the presence of

*From the Laboratory of the Detroit Board of Health.

15 per cent nitric acid or 3 per cent hydrochloric acid in alcohol. In fact it appears that the organism takes the stain better, but this may be due to the fact that the smear is of much more uniform thickness and a better view is obtained of the stained organism.

The finding of three positives among one hundred and fifty negatives does not indicate that this method is any more accurate than the usual method. It is entirely possible that the careful search of a second slide would have given an equally high result. Studies to show the relative accuracy of the Elliman-Erlandsen, Antiformin, and the Kinyoun[1] methods of digestion of the sputum and concentration of the tubercle bacilli, show a higher percentage of positive results among sputa negative by the usual method.

Agar slants were made of the supernated liquid and the coagulated material of all this series. No such tube ever showed any growth. Guinea-pigs were inoculated with those that showed the presence of acid-fast bacilli. No pigs died or showed the presence of tubercles at autopsy.

The thermal death point of the tubercle bacillus is between 55° C. and 65° C. for ten minutes.[2] In autoclaving sputum bottles, the temperature is raised to 120° C. with twenty pounds pressure for twenty minutes.

The advantages of the method are:

1. No special apparatus is necessary.
2. The outside of the bottle and carton are sterile.
3. Nothing is added to the sputum.
4. Small amount of time consumed.
5. Smears can be made more rapidly as no effort is necessary to select a particular piece of sputum.
6. The contents of the bottle are sterile.

Many of these specimens have been counterstained with picric acid.[2] When using the picric acid counterstain, the smears should be fixed and stained with carbolfuchsin in the usual way. An electric hot plate covered with asbestos board serves very well for the heating. The following solutions should be kept in wide-mouth bottles so that the smeared part of the slide can be immersed.

The smear should be immersed in one bottle after the other without washing.

*Bottle No. 1:* Saturated aqueous solution, picric acid and absolute alcohol; equal parts; about three seconds.
*Bottle No. 2:* Alcohol 60%; about three seconds.
*Bottle No. 3:* Nitric acid 15%; until properly decolorized.
*Bottle No. 4:* Alcohol 60%; about three seconds.
*Bottle No. 5:* Saturated alcoholic solution of picric acid; until a distinct yellow color is seen.

The contrast is fully as good as with the blue counterstain when the eye becomes accustomed to the change.

The advantage of the method lays in the fact that a smear five times the usual thickness can be examined because the picric acid is not an opaque stain. It is somewhat confusing at first to focus up and down through five superimposed fields, but the labor entailed is much less than making separate smears.

[1]Amer. Jour. Infec. Dis., Jan., 1914, p. 159.
[2]Hewlett: Manual of Bacteriology, Mosby Co., St. Louis, 1914.

# Slide Holder and Protector for the G. S. & E. Warming Stage*

By C. R. Eckler, Indianapolis, Ind.

ONE of the most widely useful accessories for the microscope in the field of biology is the warming stage and incubator. For observation of bacteria and yeasts in the hanging drop, for the study of malarial parasites, trypanosomas, amœbæ, or other motile organisms, for the carrying out of Widal tests, etc., such an instrument is not only of inestimable value but is almost indispensable.

A very convenient electrical warming stage and incubator is found in the No. 8, made by the Chicago Surgical and Electrical Company. As a stage incubator this instrument seems quite complete (Fig. 1), and for a description of it, quotation may be made from a booklet supplied by the Arthur H. Thomas Company, Philadelphia.

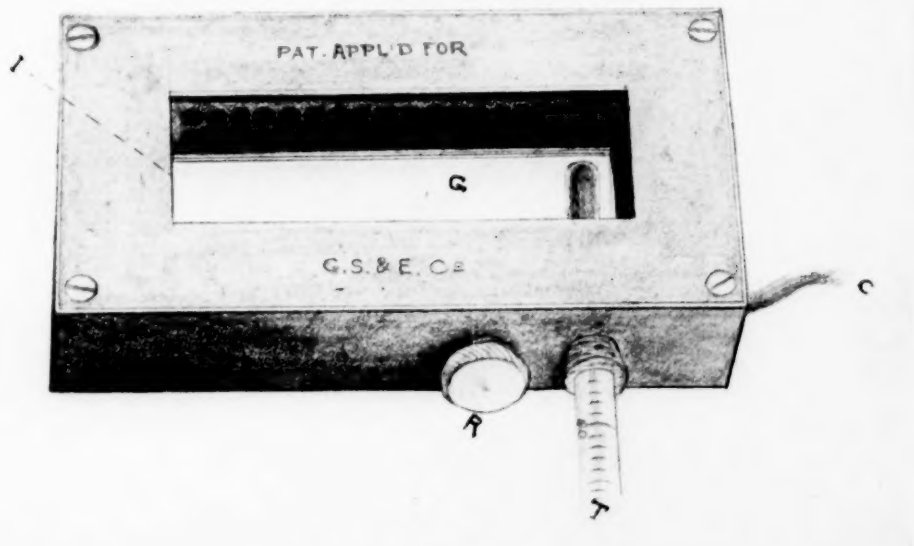


Fig. 1.—Warming stage and incubator. Mica cover for incubating chamber not shown. *C*, Cord from resistance lamp; *T*, Thermometer; *R*, Thumb-screw for regulating temperature; *I*, Incubating chamber; *G*, Glass slide at bottom of incubating chamber.

"The outside dimensions are 3½ inch. × 2 inch. × ½ inch in thickness. The incubating chamber measures 3 inch. × 1 inch × ½ inch in depth and has a removable glass bottom consisting of a regular 3 × 1 slide. The specimen to be examined is placed on this slide. The condenser may thus be brought up close to the glass, same as under ordinary conditions, permitting the use of the oil immersion lens.

"To cover top of incubator we furnish a piece of clear mica having a hole cut in center through which the lens is passed when making adjustment for

*From the Department of Experimental Medicine, Eli Lilly & Company.

the bottom slide. A rubber washer slipped over the lens is provided for sealing the opening between the lens and mica.

"By this arrangement a perfect incubating chamber is obtained, where bacteria may be observed for any length of time.

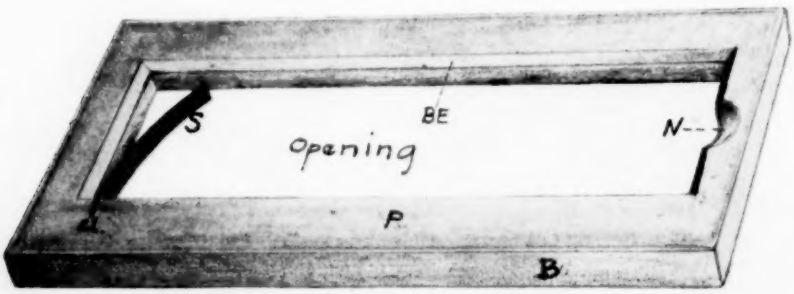


Fig. 2.—The slide holder and protector. *S*, Clock spring; *N*, Notch to admit finger nail; *BE*, Beveled edge of plate; *B*, Band 5 mm. wide about plate; *P*, Plate 4 mm. thick.

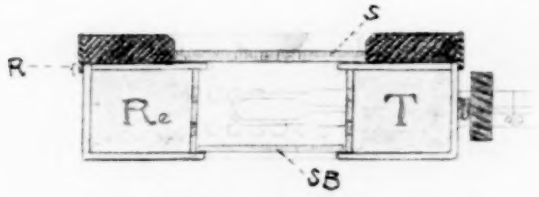


Fig. 3.—Cross-section of incubator and slide holder. *T*, Thermostat element; *Re*, Resistance coil; *S*, Regular microscopic slide; *R*, Rim which fits over incubator; *SB*, Slide at bottom of incubating chamber.

"The incubator is complete in every detail with heating element, thermometer and adjustable electro-thermostat, which automatically maintains a constant temperature inside the incubating chamber, as long as the electric current is on. This device can be adjusted for any temperature between 80° and 110° Fahrenheit and is very accurate.

"To operate, simply screw the current tap with its lamp into a 110 volt electric lamp socket and turn on the current."

This description appears to be correct except for the first paragraph in reference to the size of the incubating chamber (I, Fig. 1), which measures approximately 2⅜ inches × ¾ inch × ½ inch, instead of 3 inches × 1 inch × ½ inch, and carries a slide (G, Fig. 1) at the bottom of the incubating chamber measuring approximately 2⅜ inches × ¾ inch, instead of 3 inches × 1 inch.

This instrument may be used as well for a warming stage, and perhaps in this way, offers its greatest field of usefulness. For use in this manner it seems quite complete with one exception. Dr. A. L. Walters, using one of these instruments in the study of the endamœba of pyorrhea, suggested the need of a

slide holder and protector, there being no device on the instrument to hold the slide firmly in position during the extended observation of the motile forms, or to protect the slide from cross currents of air, or to seal any small spaces between the edges of the slide and the top of the incubator. Such spaces were found, owing to the fact that the top of the incubator was not perfectly level at all points. To fill these needs, the attachment here described, was constructed.

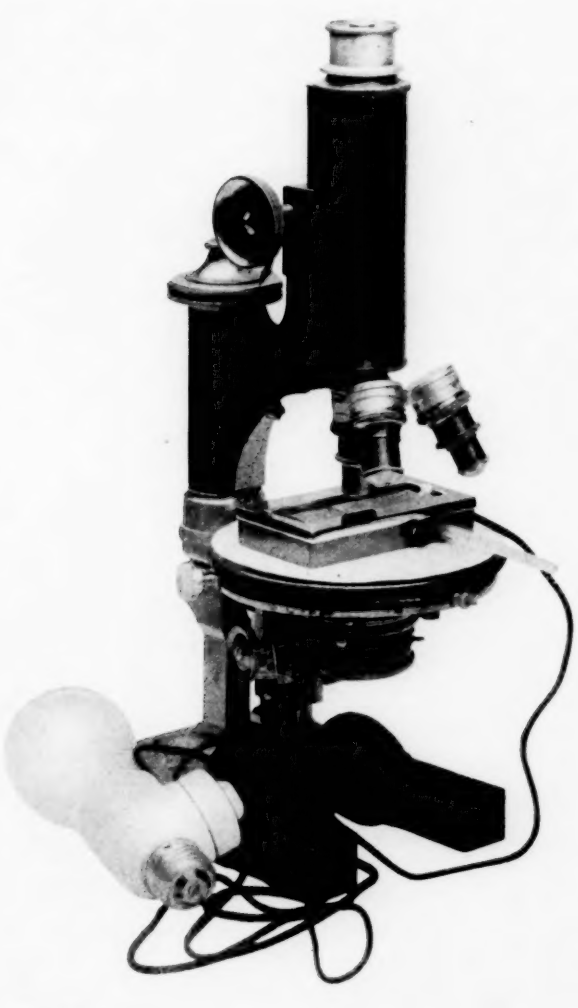

Fig. 4.—Showing instrument in position with slide inserted.

This attachment is essentially a cover for the top of the incubator (Fig. 2), made of a plate of brass 4 m.m. thick (P), which has about its edge a band of 22 gauge brass 5 m.m. wide (B) thus affording a rim at the lower edge of the plate 1 m.m. in depth (R, Fig. 3). This rim fits snugly down over the top of the incubator, gentle pressure being required to seat the plate in position, where it is held by friction. An opening (Fig. 2) is cut through the plate large enough

to admit an ordinary microscopic slide, which, when in place, rests on the top of the incubator (S, Fig. 3), closing the upper opening of the incubating chamber. The edges of the plate about this opening are beveled (BE, Fig. 2) so as not to hinder the turning of the objectives. At one end, the opposite end from which the slide is inserted, a curved piece of clock spring (S, Fig. 2) is fastened by soldering in a small slit (S1.) cut with a thread saw. This spring holds the slide firmly in place during the examination of any object, and in removing the slide, after the end opposite the spring has been released by raising with the finger nail, this spring forces the slide out of the opening to a point where it may be easily picked up with the fingers. The instrument is nickel plated.

The chief advantage of the device is that it holds the slide firmly in position, enabling the operator to observe a small object, such as a single amœba, as long as desired without danger of the slide being moved about accidentally. Forming a sort of shallow well for the slide, it seals any little spaces between the edges of the slide and the top of the incubator, and protects the slide from cross currents of air. The added weight to the incubator is useful when operated on a plain microscope stage where there are no clips to hold the instrument. The thermal capacity of the attachment aids to some extent in maintaining a uniform temperature.

The attention of laboratory workers is called to this little device through the belief that it is a valuable addition to the G. S. & E. No. 8 Incubator, when used as a warming stage, and that the advantages afforded by it would be appreciated by any one who uses one of these warming stages. It is so simple in construction, and so easily made, that anyone possessing only slight ability as a craftsman may make one for himself with the aid of a few common tools.

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## Hydrogen-ion Acidity*

By Thomas H. Kelly, M.D., Cincinnati, Ohio.

MANY attempts have been made of late years, to evolve methods by which the actual amount of free hydrogen-ions in body fluids might be determined, for the use of laboratory workers and clinicians. In these days of discussion concerning the role of colloids and their changes in hydration capacity in health and disease, an accurate knowledge of variation in hydrogen-ion content of body fluids and tissues is very necessary to a proper understanding and interpretation of many disease processes.

Of all the methods which have been used, the gas chain electro-meter method is the most nearly accurate, but its use in a clinical laboratory is practically barred because of the delicate apparatus and special training in physico-chemical methods necessary to its employment. A great many other methods are likewise too complicated to become matters of routine in clinical laboratories. Perhaps of all the methods, those of S. L. P. Sörensen and of L. J. Hender-

*From the Laboratory of the Cincinnati General Hospital.

son are among the simplest and lend themselves best to routine use, but even these are rather complicated.

In these methods standard mixtures of phosphates or acetates are made, in series containing known quantities of hydrogen-ions, and indicators are added. The fluid to be tested is properly diluted and the same indicators added, and it is then compared with the colors of the standard mixtures. This method has been very valuable and has been recently applied to the determination of hydrogen-ion acidity of the blood, to be referred to shortly.

Martin H. Fischer[1] has developed a method for determining hydrogen-ion acidity of the urine within limits of accuracy that are sufficient for clinical purposes by the use of a series of indicators graded so that their color changes take place at definite hydrogen-ion concentrations. The series which he has found to be the most useful is as follows:

| Indicator. | Concentration of H—ion at color change. | Color. | |
|---|---|---|---|
| | | Acid. | Alkaline. |
| Methyl Orange 1-2% aqueous sol. | $10^{-4}$ | Pink | Orange |
| Para-nitro-phenol 2% alcoholic sol. | $10^{-5}$ | Colorless | Greenish-yellow |
| Sives red-2 2% aqueous sol. | $10^{-5}$ to $^{6}$ | Red | Canary yellow |
| Methyl red 0. 2% alcoholic sol. | $10^{-6}$ | Magenta | Canary yellow |
| Rosolic acid 1-2% in 50% alcohol | $10^{-7}$ | Orange | Magenta |
| Phenolphthalein 1% alcoholic sol. | $10^{-9}$ | Colorless | Bluish-red |
| Thymolphthalein 1-2% alcoholic sol. | $10^{-11}$ | Colorless | Blue |

-[1]Hydrochloride of para-mono-methyl-amino-azobenzine-ortho carbonic acid.

10 c.c. of urine are placed in a clean porcelain evaporating dish which is rinsed with distilled water or the urine to be tested. The urine should be as fresh as possible. By trying two drops of each indicator on successive samples of the urine to be tested an indicator is finally found to which the urine is neutral, or is acid to one indicator in the series and alkaline to the next above it. Therefore the urine has a hydrogen-ion concentration equal to that represented by the turning point of the indicator in the first case, or lies between the turning points of the two indicators in the second. In this way a fairly accurate approximation of the hydrogen-ion concentration may be obtained.

Recently R. L. Levy, L. G. Rowntree and W. McK. Marriott[2] have published a method for the determination of the hydrogen-ion concentration of the blood. In this method they use a standard series of tubes containing mixtures[3] of 1-15 mol. solutions of primary potassium phosphate ($KH_2PO_4$) and second-

[1]Fischer, Martin H.: Oedema and Nephritis, John Wiley & Sons, New York, 1915.
[2]Levy, R. L.; Rowntree, L. G.; Marriott, W. McK.: Arch. Int. Medicine, 1915, xvi, No. 3, p. 389.
[3]Sörensen: Biochem. Ztschr. 1909, xxii, 352.

ary sodium phosphate ($Na_2PHO_4 2H_2O$) with five drops of a 0.01 per cent solution of phenolsulphonephthalein added to each tube. These mixtures are made so that each tube has a known hydrogen-ion concentration.

The determinations can be carried out on either serum, plasma, whole or defibrinated blood, and must be done in a room containing no fumes of ammonia or acids.

The blood or serum must first be dialyzed in a thin celloidin sac against an 0.8 per cent salt solution which has been tested for its neutrality. The sac permits the passage of salts but not of coloring matter or proteins.

One to three c.c. of clear serum or blood is run into the celloidin sac which has been tested for leaks and washed inside and out with salt solution. The sac is lowered into a test tube (100 by 10 m.m.—inside measurements) containing 3 c.c. salt solution, so that the salt solution is as high on the outside of the sac as the level of the blood or serum on the inside. Five to ten minutes are allowed for dialysis and then the sac is removed. Five drops of the indicator are thoroughly mixed with the dialysate and it is immediately compared with the standard series and readings made.

For the reading a good light and a white background are necessities, and readings must be made immediately. The tube most nearly approaching the color of the one to be tested is selected, and also the tube on each side. These are then examined carefully against a white background.

The authors have thoroughly tested this method and the variations in repeated determinations are surprisingly small, serum from normal persons varying between $H—10^{-7.6 \text{ to } -7.8}$. Variations toward the acid side were observed only in those cases which clinically and from the laboratory findings showed evidence of an acidosis.

Thus, for the clinical study of variations of hydrogen-ion concentration in health and disease, we have two methods which should prove valuable in the hands of workers in these fields.

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## EDITORIALS

### *New Methods for the Investigation of Breathlessness and Acidosis*

MUCH has been written in recent years concerning the supposed existence of conditions in which the reaction of the blood becomes less alkaline, that is, tends to become more acid. For the detection of this acidosis, as it is called, the most sensitive of physico-chemical methods have been adapted, and yet it has been impossible in many cases where we have every reason to expect high degrees of acidosis (as in diabetic coma) to obtain very satisfactory evidences of its presence. On the other hand, even slight disturbances in the reaction of the blood cause very distinct changes in the activity of the respiratory center, conditions associated with acidity making it more active (e. g., the breathlessness of muscular exercise, the injection of acid into animals) and conditions associated with alkalinity depressing it (the apnea produced by injecting alkali). From these observations we must conclude that the respiratory center is more sensitive to change in the reaction of the blood than the most refined physico-chemical methods.

It is obviously, however, most important for the successful investigation of the clinical conditions that are associated with some disturbance in the respiratory function, such as dyspnea and cyanosis, that we should possess a reliable method by which we may detect acidity of the blood and observe its behavior under various forms of treatment. If possible, too, we must find out the nature of the acid which is responsible for the change in blood reaction.

Thanks to the combined efforts of a group of clinical and laboratory work-

ers in London (Lewis, Barcroft, Ryffel, etc.), a great step has lately been taken in supplying us with new and apparently reliable methods. We do not propose at the present time to go into the details of this method; we defer this for a future issue of the Journal, when we hope to be able to offer some modifications which our experience with it has suggested. For the present, however, a brief description of the principle upon which the method depends is advisable, in order that we may appreciate the significance of the work which has already been done, and follow the investigations now in progress which we hope to report on from time to time.

When blood is shaken in atmospheres containing variable, but known, quantities (or pressures) of oxygen, the degree to which the hemoglobin takes up the oxygen at each pressure of the gas depends very largely on the acidity (i. e., the H-ion concentration) of the blood.[1] If the results be plotted, with the values along the ordinates representing the relative saturation of the blood with oxygen, and those along the abscissæ, the partial pressure of oxygen at which the blood was exposed, a curve, called the dissociation curve of hemoglobin or blood, is obtained. This curve has a definite shape and position in the case of normal blood. If some acid be added to the blood, the curve will be found to flatten out in proportion to the amount of acid added. Indeed, the acidity of a sample of blood can be found by comparison of its dissociation curve with that of normal blood to which known quantities of acid have been added. When the curves correspond, the bloods contain the same amounts of acid.

For practical clinical purposes, however, it would obviously be too time-consuming if, in order to plot the curve, we were compelled to employ the above described method of shaking several samples of blood at different oxygen pressures and then analyzing to see how much oxygen had been taken up at each pressure. But this is not necessary, for, thanks to the work of L. V. Hill, it is possible to find all positions of the curve for a given sample of blood by using a *constant, K,* which can be determined by finding the saturation of the blood with oxygen at *one* pressure of this gas. This constant was found by the application of mathematical principles to data furnished by a large series of observations. For determining the reaction of the blood, then, we do not require to actually plot the curve; the constant itself is sufficient. When this is low, for example, it indicates that at a given pressure of oxygen, the blood takes up an abnormally low percentage of its total possible load of oxygen, indicating that the acidity of the blood is greater than normal, and when the constant is high, for the same reason, the acidity of the blood must be low.[2]

When the blood is within the vessels its acidity is due to the presence in it of two types of acid, volatile and fixed. The volatile acid is the carbon dioxide in solution in the plasma. The fixed acids are the acid salts, lactic acid, and in some cases other acids, such as butyric. On account of the readiness with which carbon dioxide escapes from the blood after its withdrawal, it is plain that in determining the dissociation curve, or constant, we will be incurring an error on account of the loss of carbon dioxide. We will, in other words,

[1] It is also influenced by salts, but this factor may for the present be disregarded.

[2] Barcroft suggests the following terms to express these conditions: (1) meionectic—where K is low and the acidity therefore great; (2) pleonectic—where K is high and the acidity small; (3) mesectic—when K is normal.

find the blood to be less acid than it should be. In order to find the true degree of acidity we must shake the blood in an atmosphere containing the same pressure of carbon dioxide as that which exists in the patient's blood plasma.

To make the method of value, therefore, for measuring the actual H-ion concentration of the blood, we must know the carbon dioxide tension. This is comparatively an easy thing to determine, for, thanks to the work of Haldane and his pupils, we know that the percentage of carbon dioxide in the alveolar air is directly proportional to the tension of this gas in the blood plasma. All we have to do, therefore, is to take a sample of alveolar air and analyze it for its percentage amount of carbon dioxide, and then to add this amount of carbon dioxide to the atmosphere with which the blood is shaken in determining the dissociation constant.

We have described the way in which the method may be used for determining the actual H-ion concentration, but now we must consider its application in detecting *the exact nature of the acid* which may be responsible for hyperacidity. This is done by an application of the same principle and may perhaps be best illustrated by taking a concrete example. Let us suppose that the dissociation constant shows us a given blood, shaken in the absence of carbon dioxide, to be hyperacid (i. e., K low). The question is, of what nature is the acid that is present in excess? We have seen that it may be either volatile or fixed acid. If volatile acid is the cause, then we should expect, from Haldane's principle, that an excessive percentage of carbon dioxide will exist in the alveolar air. Such will actually be found to be the case during the earlier stages of muscular exercise, but in pathological conditions (for example, the so-called uremias) it will usually be found that there is no evidence of an increased amount of carbon dioxide in the alveolar air, indeed, it is usually lower, so that the hyperacidity of blood must be due to fixed acid.

Or let us take the case of diabetic coma. Shaken in an atmosphere that is free of carbon dioxide, the blood will be found to be hyperacid, but if the alveolar $CO_2$ content is determined, it will be found subnormal; often markedly so. The conclusion is that the hyperacidity of the blood in diabetic coma is not due to an excess of carbon dioxide, but to an excess of fixed acid, which has displaced much of the carbon dioxide.

To illustrate the value of the above method, a few of the results which have already been obtained by Lewis, Barcroft, etc., may be of value. In the dyspnea which occurs in mitral stenosis of young rheumatic girls, the blood, freed from carbon dioxide, has a normal reaction, but the alveolar air contains an excess of carbon dioxide. The dyspnea in these cases is therefore due to a hyperacidity caused by a mechanical defect in the ventilation of the lungs—a defect which interferes with the proper excretion of carbon dioxide.

In another group of cases which would commonly be diagnosed as uremic, and in which dyspnea rather than cyanosis is the pronounced symptom, the blood, freed from carbon dioxide, is found to have a high acidity ($K$ of low value). On the examination of the alveolar air, however, a low tension of carbon dioxide is found present. Evidently, then, the acidity is due to the excessive presence of non-volatile acids.

Another instance of the use of the method is in diabetic coma. As already

mentioned, in this case the carbon dioxide-freed blood has a very high acidity, and yet the alveolar $CO_2$ tension is very low. And, lastly, in cases of mountain sickness the blood samples show high acidity, but the alveolar air, a low carbon dioxide tension.

Before this work can be considered as finally completed, we must succeed in showing that there is really an excessive amount of fixed acid present in the blood. We must isolate this acid and see what it is. Although this part of the problem is being vigorously attacked, it has not as yet been possible to succeed in showing that all of these cases having high fixed acidity really contain an excessive amount of lactic acid in the blood. Sufficient evidence has, however, been accumulated to show that the above inferences are probably correct.

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—*J. J. R. M.*

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## *The Welch Bacillus and Disease*

THE recent frequent reports of so-called "gas bacillus" infections among the soldiers in France has lent a peculiarly timely interest to the monograph of the Rockefeller Institute on "Studies in Bacillus Welchii, with Special Reference to Classification and to Its Relation to Diarrhea," by Dr. J. P. Simonds. There has been endless confusion in the classification of the so-called aerogenes capsulatus organisms, a group which has been known in different countries by a large variety of names. Its first description is probably that by Welch and Nuttall in 1892, who gave it the name *B. aerogenes capsulatus,* by which name, or briefly *Welch bacillus,* it is most commonly designated by American bacteriologists. Similar or identical organisms are the *B. phlegmonis emphysematosae* of Fraenkel, the *B. enteritidas sporogenes* of Klein, the *B. perfringens* of Veillon and Zuber, and the *Granulobacillus saccharobutyricus liquefaciens immobilis* of Schattenfroh and Grassberger, and a number of others less prominent in the literature. The task of classifying these organisms is one of great technical difficulty, and, as in so many other groups of bacteria originally described as a single species, we are now learning that instead of finding complete identity of individual isolations, one with another, we can merely draw a circle about a correlated group, recognizing close relationship morphologically, culturally, and in relation to infections of man and animals. After a very careful study of many different strains, Simonds comes to the conclusion, that the Welch bacillus, so-called, is roughly identical with those mentioned, including also the bacilli once associated by Achalme with rheumatic infections. The term *B. Welchii,* he concludes, does not represent a fixed species but a closely related group of bacteria not yet fully classified even by his own extensive studies.

It is hard to determine in the case of organisms of such varied activities exactly what can be regarded as a cardinal characteristic important for classify-

ing purposes. The organisms treated of in this group are all large Gram-positive, non-motile bacilli, with rounded ends, rarely occurring in chains, and anærobic. Spore formation is inconstant and occurs only in an alkaline medium. When fermentable sugars, and consequently free acid, are present, no spore formation takes place. Milk is fermented with the formation of butyric acid. The intravenous injection of animals, especially rabbits, usually produced death with an enormous swelling of the body by the formation of gas, which burns with a pale blue flame. Capsules may be seen when the smears are made directly from animal tissues, but are almost universally missed in organisms taken from culture.

As to minor cultural characteristics, so many variations are observed that it is hardly worth while to summarize them in a brief review of Simond's monograph. It is extremely interesting that, though a pathogenic anærobe, no one has so far been able to show satisfactorily the production of a true exotoxin, though such a claim has been made several times. Poisonous products that have been obtained from cultures have not conformed with the characteristics of true exotoxins as we recognize them now. Moreover, the reaction of toxin-containing filtrates, as Simonds points out, has been almost always acid, and McCampbell and others have suggested that the toxicity of such cultures is due to the presence of butyric acid. It is interesting in this connection also that Herter, who gave a great deal of attention to the presence of these organisms in the bowel and attributed to them etiological relationship with many intestinal disorders, believed that the diarrhea following intestinal putrefaction was due to a very large extent to the irritation produced by ammonium butyrate, the Welch bacilli of the bowel being responsible for the appearance of the butyric acid.

The search for endotoxins, too, seems to have been unsuccessful, and hemolysins have been irregularly present in cultures studied by various investigators.

Great differences in virulence have been observed in the study of various strains. A good many of the strains seem to have great pathogenicity for the ordinary laboratory animals, especially for guinea-pigs and rabbits. Yet certain non-sporulating forms have shown little or no virulence. However, variation in virulence seems to fluctuate considerably according to the culture medium and the symbiotic conditions under which the organisms have been cultivated. In man, fortunately, there seems to be a relatively powerful resistance against Welch bacillus infections. In fact, many investigators have believed that the Welch bacillus is primarily a saprophyte and requires the presence of dead tissue or physiological injury before it can penetrate and thrive in the human body.

Very interesting is the extensive review of the literature in which this organism or varieties of it have been found associated with human lesions. It has been observed in gas cysts of the brain, in "gangrenous" pneumonia, in appendix abscesses, in puerperal sepsis after abortion, in general septicemia, and in many other conditions. However, in many of these cases it may be quite reasonable to question the primary character of the "gas bacillus" infection, and in others again, the Welch bacillus may be regarded as an ante-mortem invasion, a supposition strengthened by the study of terminal infections made by Flexner, in which such a possibility is plainly demonstrated. Thus, while the Welch bacil-

lus may unquestionably invade the human body and do much injury, and even be probably regarded in many cases as the direct cause of death, its invasion in many of these cases must be regarded as not a primary invasion, but as one associated with and made possible by either traumatic injury or the co-operation of other invasive germs such at streptococci, staphylococci, and others. There may, of course, in addition to these be rare instances in which the Welch bacillus, owing to excessive virulence of the strain or relatively low resistance of the infected individual becomes the primary invader. It is easy to understand under these conditions, why in warfare, severe trauma associated with the carrying of soil and often feces-contaminated fragments of clothing into the wound would form ideal conditions for the production of Welch bacillus infections.

The most interesting chapter in the pathogenicity of the Welch bacillus is its relation to intestinal disease. Simonds confirms by his own work the work of many others which has shown that the Welch bacillus may be regarded as a normal inhabitant of the intestines of man. In nineteen babies under one year of age he found Welch bacilli in the stools of eight. He points out that it has been found even in nursing infants by a number of investigators. His own cases were feeding cases with practically no digestive disease and without pus or blood in the stools in any of them. Fluctuations in the abundance of Welch bacilli in the stools of adults, Simonds attributes very largely to daily variations in diet. He thinks it quite likely that the bacillus may give rise to a fairly definite type of diarrhea. He summarizes the arguments brought out in favor of this, as follows:

1. In cases of this kind spores are found in great numbers in the stools.
2. Patients with diarrhea associated with excessive number of gas bacilli are made worse by feeding them a diet rich in carbohydrates and show improvement when the diet is changed to one of pure protein with or without buttermilk.

The relation of the organism to pernicious anemia, first pointed out by Herter, Simonds dismisses with a rather brief discussion, coming to the conclusion that no positive statement can at present be made concerning the relation of the bacillus to this disease. He isolated four strains from stools of patients with pernicious anemia, one of which caused no hemolysin at all, two others being very slightly hemolytic. Of course, the anemia of pernicious anemia is not necessarily due to absorption of hemolysin and might be regarded as secondary to injuries to the digestive tract and the digestive processes, coincident to the constant presence of large numbers of these organisms in the intestinal contents. However, with Simonds, it seems to us from a reading of the literature that no satisfactory relationship between the organism and the disease has as yet been established.

In spite of the fact that the Welch bacillus does not produce spores in culture media in the presence of fermentable substances or of free acids, nevertheless under the conditions of symbiotic growth in the intestine Simonds shows that sporulation is possible even in the presence of fermentable carbohydrate provided that the symbiotic flora is such that the acidity of the mixture does not rise above three per cent, measured in normal acid. Taking this into consideration Simonds concludes that the number of spores of *B. Welchii* in the

stools is a reasonably accurate index of the number of actively fermenting, disease-producing organisms of this type higher up in the intestine.

Although the subject of Welch bacillus infections is by no means closed by Simond's monograph, it nevertheless goes far to bring order out of chaos, and it is quite plain that no conclusions concerning this group can be attained without the comparative study of a large number of different strains.

—*H. Z.*

## *Carbon Dioxide and Blood Pressure*

THE mechanism which controls blood pressure has supplied many workers with interest through many series of experiments. The facts relating to blood pressure are chiefly two; i. e., it may be modified by alteration in the peripheral circulation, or by increase in the force of the heart beat.

The physiologic method of modifying the peripheral vascular pressure is one which modifies the condition of contraction of the muscle of the smaller arteries. If they are contracted, the blood pressure rises; if they are dilated, it falls. The cardiac output is conditioned by the state of the heart muscle and by the cardiac intake. The former is governed primarily by the coronary circulation; the latter, by the conditions in the peripheral circulation. When increased work is thrown upon the myocardium, the coronary vessels dilate and so the nutritive conditions in the myocardium are improved. The dilatation of the coronaries is determined by chemical means; i. e., by the metabolic products in the blood, mainly, perhaps, carbon dioxide.[1] There seems to be no doubt that acid products of metabolism are the main conditions underlying vascular dilatation. This would obviously tend to the conception that under conditions of increased metabolism, the blood pressure should fall—which it does provided the $CO_2$ tension passes a certain stage. Within certain limits, however, increased $CO_2$ tension results in a rise of blood pressure.

In 1909 Kaya and Clark showed that an increase of $CO_2$ tension in the blood was followed by increased blood pressure, and that decreases in this tension were followed by proportionate decreases in blood pressure.

Cathcart and Clark later showed that deep anesthesia inhibited this mechanism, and Jerusalem and Starling found that when they used an isolated heart-lung preparation an increase of $CO_2$ caused slowing of the heart, while at the same time the ventricular output was increased by addition of $CO_2$ up to 8 per cent of an atmosphere. Itami also found that with 5-10 per cent of $CO_2$, the blood pressure rose, and von Anrep demonstrated that if the adrenals were removed or isolated, the $CO_2$ rise of pressure did not occur. Cannon and Hoskins and Czubalski observed that in asphyxia there was increased adrenalin in the blood.

Cathcart and Clark[2] have recently reported experiments which were planned to discover the mechanism of the process indicated in the above mentioned paragraphs. They found that in the intact animal an increase of $CO_2$ is followed by an increase of blood pressure. In their experiments they used 12 per cent $CO_2$. The heart was always slowed. When pure air was substituted for the

[1]Markwalder and Starling: Jour. Physiol., 1913 (47) 275. (For other references, cf. Woolley: Jour. Amer. Med. Assoc., 1914 (63) 2279, and Centralb. f. all. Path., 1913 (26) 217.)
[2]Jour. Physiol., 1915 (49) 301.

$CO_2$ the cardiac amplitude rapidly returned to normal and the blood pressure fell gradually. If the animal was decapitated, the cardiac rate and amplitude, and the blood pressure fell. Section of the vagi alma did not prevent a rise of pressure.

These experiments make it quite evident that some part is played in the production of increased blood pressure by the higher centers, and that this influence is removed by deep anesthesia and decapitation, but not by section of the vagi. In view of the results of von Anrep, Cathcart and Clark treated animals with nicotin and then administered $CO_2$. Under these circumstances there was no increase in pressure, which indicated that, as Cannon has said, adrenalin plays a part in the regulation of blood pressure.

From these results one is justified in believing that increased $CO_2$ content in the blood increases the adrenalin content of the blood and this in time causes vascular constriction and increased blood pressure, associated with slowing of the heart and increased amplitude. The results of Cathcart and Clark indicate that the mechanism may be broken by removing the influence of the sympathics upon the adrenals, or by interference with a central mechanism which, they suggest, is in the medulla. Whatever the mechanism is, small doses of adrenalin given intravenously will still produce their characteristic reaction.

All this is very interesting from the standpoint of organic chemical correlations. As work is done by the tissues of the body, especially the muscles, the acid products of metabolism enter the blood stream and being carried to the respiratory center, stimulate it and so produce an increased respiratory rate. This, in its turn, tends to prevent an over-increase of $CO_2$ in the blood. At the same time the moderate increase of $CO_2$ which appears in the blood stream acts, by way of the adrenal mechanism, in producing increased peripheral resistance, increased blood pressure, and slowing of the heart, and thereby increases the ventilation of the tissues, and increases the facilities for washing them out. In a recent report Boothby[3] shows the relationship by a series of experiments and the results of these lead him to the conclusion that one factor; i. e., the total acidity of the blood, or the hydrogen-ion concentration in the arterial blood, is the governing cause of both circulatory and respiratory activities.

—*P. G. W.*

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## *Bismuth Poisoning*

THE importance of bismuth in medicine has greatly increased within the last few years. Various manufacturing interests bearing this extended use in mind have now placed on the market a large number of new compounds containing the metal. As a general rule the value of these in medicine depends on their difficult solubility. For while a certain rather limited value attaches to these preparations as antiseptics after they pass into solution either in the tissue fluids or in other menstrua, we are as yet practically entirely ignorant of any special therapeutic value which these compounds may possess over various other similar rather insoluble substances. They are easily accessible and serve

[3]Amer. Jour. Physiol., 1915 (37) 383.

a number of purposes well and have therefore come more and more into use.

The older uses of the salts of bismuth as dusting powders for ulcers, for gastric catarrh and gastric ulcer and for diarrhea or other inflammatory conditions of the mucosa of the alimentary tract have more recently been greatly overshadowed by the introduction of bismuth salts into x-ray work and by their use in the diagnosis or treatment of chronic abscesses or sinuses. For this latter use the medical profession is mainly indebted to Doctor E. G. Beck, of Chicago, who has opened up a practically new field in modern therapeutics by the introduction of a paste[1] composed essentially of 33 per cent of a bismuth salt (usually the subnitrate, $BiONO_3+xH_2O$) and 66 per cent of vaseline. Occasionally wax[2] is used in the paste. Soluble bismuth preparations are of but little use in the medicine for they are very corrosive. Applied locally to ulcerated or abraded surfaces the common bismuth salts such as the subnitrate or subcarbonate $[(BiO)_2CO_3+xH_2O]$, gradually take up a certain portion of the tissue fluids and form a protective pellicle or crust which may expedite the process of healing. A mild antiseptic action and some astringency are also manifested by the metal under these conditions.

Within the last few years a special interest has been developed in this subject by the occurrence of a number of cases of bismuth poisoning. Clinically, these have usually been due either to absorption from the alimentary canal following ingestion of the metal for the purpose of x-ray diagnosis or to absorption from a sinus or abscess injected with Beck's paste.

Experimentally only a limited amount of work has been done on the pharmacological action of the metal. There appear to be a great many points on which further careful experimental work is greatly to be desired. Under most conditions the metal is only a feebly active body and this perhaps accounts for the little consideration which has generally been accorded to it by pharmacologists. The work which has been done, however, serves to give some insight into its pharmacological and toxicological properties. In animals acute poisoning may readily be produced, or the slow absorption of small quantities over some time may lead to chronic intoxication. If a soluble double salt such as the tartrate of sodium and bismuth be injected into an animal, there will be produced an acceleration of the respiration, irregular clonic and tonic convulsions followed by prostration, incoordination and weakness. The heart is first slowed and later becomes irregular and weak. The central nervous system is first stimulated and later paralyzed. This stimulation of the central nervous system, which appears to be most marked in the medulla, is of peculiar interest in a metallic substance. There is a progressive fall of blood pressure as the heart becomes weak and irregular, and the vasomotor centre is more and more depressed.

The chronic form of poisoning appears to resemble the symptoms produced by prolonged absorption in man quite closely. The condition here reminds one especially of a mild form of chronic mercury poisoning with some features resembling chronic lead intoxication. The alimentary tract is first affected and anorexia, nausea and vomiting, diarrhea, increased salivation and soreness of the mouth, tongue and gums come on. A peculiar narrow violet-black line may

[1]Beck, E. G.: Annals of Surgery, 1914, lix, p. 145.
[2]Jensen, Theodor: Muenchener Medizinische Wochenschrift, 1913, lx, June 3, p. 1202.

appear on the margins of the gums as one of the first symptoms. This is liable to persist for a considerable period. If the case be mild, this may be the only marked symptom present. The urine often contains bismuth and may be of a dark color. If the intoxication proceeds the stomatitis becomes more and more severe. Ulceration of the gums and buccal mucosa ensues and peculiar violet or blackish spots appear over the surface. These may become infected and lead to fever and general systemic disturbances. The swollen gums may bleed and the teeth may become loosened or fall out. White diphtheritic-like membranes have been described as appearing on the gums. Various forms of convulsive manifestations may appear from time to time, and pain and difficulty are experienced in swallowing. Albuminuria is generally present especially if the case is severe.

From the alimentary canal bismuth appears to be absorbed only with difficulty and in very small amounts under ordinary conditions, so that poisoning from this source by bismuth itself is rare. When taken into the stomach or intestine the metal is supposed to form a thin protective covering over the mucosa and thus protect ulcerated or abraded surfaces. From various experimental and clinical observations it appears that absorption of the substance is much more likely to occur if a large area of raw or granulating surface is coated with the metal than if it comes in contact only with the normal mucosa. This apparently also holds true to a certain extent in the injection of sinuses and abscesses, for if these are old chronic lesions and no probing or cutting of the tissues has been carried out so that the paste cannot come into immediate contact with a fresh surface of the tissue, then absorption and poisoning are much less likely to occur. In 1887 Dalché and Villejean[3] showed that pure bismuth salts were toxic. They gave a dog daily 10 grammes of the subnitrate without observing any ill effect, but when the salt was put on a raw surface of any extent, intoxication often followed.

A number of cases of poisoning have been reported when bismuth subnitrate was used and which manifested symptoms of nitrite poisoning alone. In these cases the salt evidently became decomposed and nitrites became formed from the nitrate radicle. This is, of course, a wholly different thing from bismuth poisoning. An instructive report on this point has been made by Jensen.[4] The symptoms in these cases consist of restlessness, chilliness, weakness and loss of appetite, nausea or vomiting, and headache with a small, weak, irregular but rapid pulse. The temperature is subnormal or fever may rarely appear. There is tingling or numbness in the fingers, dyspnea and cyanosis and great muscular weakness. Methaemoglobin may be produced in the blood by the action of the nitrite. It has been suggested by Jensen and others that in these cases certain bacteria may be especially active in splitting off the nitrate radicle from the bismuth. In bouillon cultures of colon bacilli and of staphylococci (but not of streptococci) it was found that nitrates were formed when bismuth subnitrate was added to the cultures. And the suggestion has therefore been made that the subnitrate should not be used in injecting sinuses, etc., if previous bacteriological examination shall have shown the presence of colon bacilli or

[3]Lancet, 1913, Vol. 1, April 12, p. 1039. Arch. gen. de. Med., 1887, ii, p. 129.
[4]Loc. cit. Also, Böhme, A.: Archiv. für experimentelle Pathologie und Pharmakologie, 1907, lvii, p. 441.

staphylococci. Perhaps the formation of moderate amounts of nitrites by these organisms in the alimentary canal might be of much less serious import than the production of a corresponding amount in a fistula or sinus. It would seem safer as a rule to use the subcarbonate in preference to the subnitrate.

It has further been suggested by Rost[5] and Wacker[6] that the active (therapeutically valuable) portion of Beck's paste may be the vaseline and not the bismuth at all. Some evidence in this direction was apparently obtained by the production of favorable results after the use of vaseline alone, "American" vaseline being more active in this direction than that obtained in Germany, presumably because the former was more impure and irritating. The well-known action of paraffin-related substances in producing skin lesions is referred to by Wacker in this connection.

Under normal conditions it appears that but little bismuth is absorbed from the alimentary canal although occasionally traces may be found in the urine after ingestion of the metal. The excretion occurs mainly through the kidneys and the alimentary canal. In the kidney may be seen that inflammatory condition usually produced when that organ has to excrete metallic substances foreign to the body, the "metallniere," or metal kidney, of German writers. The stools take on a black color which has generally been claimed to be due to the formation of the sulphide of the metal in the bowel, although it has been suggested that this is due to reduction of the subnitrate in the intestine. The sulphide is very insoluble and Meyer and Steinfeld[7] have maintained that it is precipitated not only within the lumen of the bowel, but also in the capillaries and lymph spaces of the mucosa where hydrogen sulphide penetrates in traces from within the bowel. This causes the formation of minute emboli which clog the capillaries and lead to localized ulceration and gangrene. These authors believed from experimental observations that bismuth was excreted throughout the length of the alimentary canal but mainly in the large intestine where a dense black coloration of the entire thickness of the wall of the cecum and colon could be seen postmortem. This observation reminds one of the excretion of iron. If in addition sulphur preparations were given to animals treated with bismuth salts, then blackening or even ulceration of the mucosa occurred in the stomach and small intestines, also thus indicating excretion of the metal in these regions.

The treatment of bismuth poisoning consists chiefly in removal of the cause. Severe cases of true chronic bismuth poisoning are scarcely seen at present because of the early diagnosis of such cases. Severe nitrite poisoning, however, may occur for it is much more rapid in its onset and may be fairly marked before the patient is seen by the physician. These cases are, however, apparently exceedingly rare. In case symptoms of poisoning from injection of bismuth paste appear, Beck[8] recommends that the paste be removed as soon as possible. The best way to do this is by washing out the cavity with warm olive oil. The sterile oil is injected and retained for twelve to twenty-four hours, in order to produce an emulsion, which should be withdrawn by means of suction. After

[5]Rost, Franz: Muenchener Medizinische Wochenschrift, 1913, lx, Oct. 14, p. 2281.
[6]Wacker, L.: Muenchener Medizinische Wochenschrift, 1913, lx, Dec. 2, p. 2674.
[7]Meyer und Steinfeld: Archiv. für experimentelle Pathologie und Pharmakologie, 1886, xx, p. 40. Steinfeld: Wirkung des Wismut, Inaug. Diss. Dorpat, 1884.
[8]Beck, E. G.: Loc. cit., p. 156. Also Journal of the American Medical Association, 1909, Jan. 8. Warfield, Louis M.: American Journal of the Medical Sciences, 1912, cxliv, p. 647.

its removal all symptoms should promptly disappear. Scraping out the paste with a scoop is a dangerous procedure, because it opens fresh channels for absorption.

In Röntgen-ray[5] examinations the ingestion of large amounts of bismuth has sometimes led to the formation of large concretions in the stomach or intestines. Possibly this may occasionally be associated with an increased formation of the sulphide of the metal.

—*D. E. J.*

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## *The Glucose Content of the Blood*

WITHIN the last few years the chemistry of the blood has been receiving increasing attention. Until recently the methods were so complicated and laborious and required such large quantities of blood, that they could not be employed by the clinician. With the growing importance of the subject, however, simplified methods have been devised which permit of repeated determinations, owing to the fact that only small amounts of blood are required, without sacrificing accuracy. Thus Folin and Denis[1] have described methods for the determination of urea, ammonia, non-protein nitrogen and uric acid; Bang, Shaffer,[2] Kowarsky and others for the determination of glucose; Marriott[3] for the estimation of "acetone bodies;" and Bloor[4] for fat. These methods are now being employed in the clinic. The field is so comparatively new that the data at hand are at present insufficient for definite conclusions in most instances.

The variety of methods for determination of blood sugar is greater than for most other substances of the blood, and as a result of the differing technics employed, comparison of the work of different observers is misleading at times. In any of the methods employed, it is necessary to remove the proteins. This is accomplished with least loss of glucose by combined heat-coagulation and the Michaelis-Rona colloidal iron precipitation, as Shaffer[3] has shown. In those methods for example, in which the proteins are removed by precipitation with alcohol, there is definite loss of sugar. Shaffer's method is rapid, accurate and requires only 5 c.c. of blood for a determination. Strouse[6] has recently described a modification of Kowarsky's method which is very similar to Shaffer's, but which is carried out with only 0.5 c.c. of blood. Should it prove to be equally accurate, the smaller quantity of blood needed (which may be obtained from a puncture wound) would be a decided advantage.

With a given method, even though the results may not be absolutely correct, still they are of value comparatively, showing variations of glucose content from time to time in the blood of the same individual, and furnishing a basis for comparing the glucose concentration of the blood of normal individuals with that found in disease.

[5]Cannon, W. B.: The American Journal of Physiology, 1898, i, p. 359; 1902, vi, p. 251.
[1]Jour. Biol. Chem., 1912, xi, 527.
[2]Ibid., 1914, xix, 285.
[3]Ibid., 1914, xviii, 507.
[4]Ibid., 1914, xvii, 377.
[5]Loc. cit.
[6]Bull. Johns Hopkins Hosp., 1915, xxvi, 211. (For a comparison of the methods of Bang and Bertrand, see Fitz. Arch. Int. Med., 1915, xiv, 133.)

Studies on the blood of normal individuals have disclosed the fact that diet is of considerable importance. Thus, a value which is normal for a fasting patient may be greatly increased after a meal containing sugar or starch, whereas protein and fat are without appreciable effect on the percentage of glucose in the blood. This fact has been emphasized by Bing and Jakobsen[7] and by Strouse. The latter also made the interesting observation in a patient with obstinate furunculosis but without glycosuria that the glucose concentration following a meal containing carbohydrates was unusually high; the placing of the patient on a strict carbohydrate-free diet was followed very promptly by cure.

Aside from the response to carbohydrates in the food, Kahler[8] reports observations which seem to show that there is also a physiological rise in the concentration of blood glucose in women during menstruation.

In disease a few scattered observations are recorded, as yet insufficient to be of great value. Only a part of them are cited below.

Purjesz[9] finds that with increased activity of the thyroid gland the blood glucose is lower than normal. Bing and Jakobsen,[10] using Bang's method, report similar findings. Administration of the "infundibular part of the pituitary gland" was followed by an increased concentration of glucose. In pancreatic disease Bing and Jakobsen report increased percentage of blood glucose. In Addison's disease Purjesz found a marked decrease in glucose, while Schirokauer[11] has found normal values on two occasions in one patient.

Increase of blood glucose has been noted in hypertension. Bing and Jakobsen report cases of nephritis unassociated with hypertension, which also showed an increase in blood glucose content.

Menke,[12] using Bang's method, reports observations on the blood of diabetes. Hourly determinations of the glucose content of the blood showed great variations which, without regard to the severity of the disease, seemed to depend on the taking of food and the activity of the kidneys; a fall in blood sugar was found to be coincident with excretion of sugar by the kidneys. Surprisingly high values were often encountered in fasting patients, but it was Menke's impression that the differences in concentration thus obtained do not furnish an accurate index of the severity of the disease. A comparison of the blood glucose curve after ingestion of like quantities of wheat and oatmeal showed no differences either in the height or rapidity of the rise. Bing and Jakobsen found no direct relationship between the degree of hyperglycemia and glycosuria in diabetes.

The group of cases of so-called renal diabetes is being enlarged through the study of the glucose content of the blood. Novak, Porges and Strisower[13] have investigated the spontaneous glycosuria of pregnancy. In seven consecutive cases, they found that the glucose content of the blood was not increased, and that the excretion of sugar was largely independent of the diet. With the

[7]Deutsch. Arch. f. klin. Med., 1914, cxiii, 571.
[8]Wiener klin. Wchnschr., 1914, xxvii, 417.
[9]Ibid., 1913, xxiv, 1420.
[10]Loc. cit.
[11]Berlin klin. Wchnschr., 1911, xlviii, 1505.
[12]Deutsch. Arch. f. klin. Med., 1914, cxiv, 209.
[13]Deutsch. med. Wchnschr., 1912, xxxviii, 1868.

carbohydrates eliminated from the food, sugar was still excreted, but the addition of a considerable amount of carbohydrates to the diet did not cause a corresponding increase in the sugar of the urine. Salomon[14] has reported observations on renal diabetes in non-pregnant patients. He finds that the concentration of glucose in the urine is usually under one per cent and that the excretion of sugar is only slightly affected by diet. The blood glucose concentration is usually under 0.1 per cent. After administration of 100 gms. of glucose to the fasting patient, usually only from 1 to 7 per cent of this is excreted in the urine. With the administration of glucose there is a hyperglycemia which persists for a few hours.

It is altogether probable that the results of the study of blood glucose will greatly enrich clinical medicine, not only from the standpoint of more accurate diagnosis and prognosis, but also of treatment.

—*R. S. M.*

[14]Ibid., 1914, xl, 217.